

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.**

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
25 January 2001 (25.01.2001)

PCT

(10) International Publication Number  
**WO 01/05793 A1**

(51) International Patent Classification<sup>7</sup>: C07D 487/04,  
A61K 31/55, C07C 321/30, 317/32, C07D 223/12 //  
(C07D 487/04, 223:00, 209:00)

(74) Agent: STEIN, Bruce; Intellectual Property Legal Ser-  
vices, Pharmacia & Upjohn Company, 301 Henrietta Street,  
Kalamazoo, MI 49001 (US).

(21) International Application Number: PCT/US00/16322

(22) International Filing Date: 11 July 2000 (11.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/144,574 19 July 1999 (19.07.1999) US

(71) Applicant (for all designated States except US): PHAR-  
MACIA & UPJOHN COMPANY [US/US]; 301 Henri-  
etta Street, Kalamazoo, MI 49001 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): JACOBSEN, E., Jon  
[US/US]; 3701 Willow Lake Drive, Kalamazoo, MI 49008  
(US). HENDGES, Susan, K. [US/US]; 376 Timber Ridge  
Drive, Kalamazoo, MI 49006 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,  
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,  
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,  
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,  
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,  
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

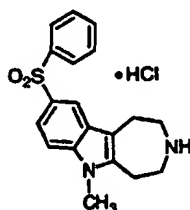
Published:

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

WO 01/05793 A1

(54) Title: 1,2,3,4,5,6-HEXAHYDROAZEPINO[4,5-b]INDOLES CONTAINING ARYLSULFONES AT THE 9-POSITION



(57) Abstract: The present invention is substituted 9-arylsulfone-1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles (X) and unsubstituted 9-arylsulfone-1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles (XI) such as the compounds of EXAMPLE (13), which are useful in treating depression, obesity and other CNS disorders.

## 1,2,3,4,5,6-HEXAHYDROAZEPINO[4,5-b]INDOLES CONTAINING ARYLSULFONES AT THE 9-POSITION

CROSS-REFERENCE TO RELATED APPLICATIONS

None.

BACKGROUND OF THE INVENTION1. Field of the Invention

The present invention is substituted 9-arylsulfone-1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles (X) which are useful for treating anxiety, depression and other CNS disorders in humans and animals.

2. Description of the Related Art

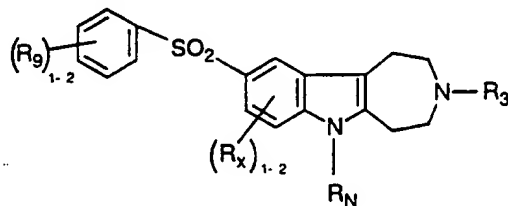
US Patent 3,652,588 discloses 6-alkyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles which were useful for tranquilizing and sedating mammals to suppress hunger in mammals. This document discloses that there can be substitution at the 9-position. However, those substituents are limited to hydrogen, alkyl, alkoxy and halogen.

US Patent 3,839,357 discloses 6-benzyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles which were useful for tranquilizing mammals. This document discloses that there can be substitution at the 9-position. However, those substituents are limited to hydrogen, alkyl, alkoxy and halogen.

US Patent 3,676,558 discloses 6-alkyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles which were useful to suppress hunger in mammals. This document discloses that there can be substitution at the 9-position. However, it is limited to hydrogen, alkyl, alkoxy and halogen.

SUMMARY OF INVENTION

Disclosed is a 9-arylsulfone of the formula (XII)



where R<sub>3</sub> is:

- (1) -H,
- (2) C<sub>1</sub>-C<sub>4</sub> alkyl,
- (3) C<sub>0</sub>-C<sub>4</sub>-φ where the -φ substituent is optionally substituted with 1 or 2
- (a) -F, -Cl, -Br, -I,

(b)  $-O-R_{3.1}$  where  $R_{3.1}$  is:

-H,

$C_1-C_4$  alkyl,

$-\phi$ ,

5

(c)  $-CF_3$ ,

(d)  $-CO-NR_{3.2}R_{3.3}$  where  $R_{3.2}$  and  $R_{3.3}$  are -H and  $C_1-C_4$  alkyl, and where  $R_{3.2}$

and  $R_{3.3}$  are taken with the attached nitrogen atom to form a ring selected from the group consisting of 1-pyrrolidinyl, 1-piperazinyl and 1-morpholinyl,

(e)  $-NH-SO_2-R_{3.4}$  where  $R_{3.4}$  is -H and  $C_1-C_4$  alkyl,

10

(f)  $-NR_{3.2}R_{3.3}$  where  $R_{3.2}$  and  $R_{3.3}$  are as defined above,

(g)  $-NR_{3.4}-CO-R_{3.4}$  where  $R_{3.4}$  is as defined above,

(h)  $-SO_2-NR_{3.2}R_{3.3}$  where  $R_{3.2}$  and  $R_{3.3}$  are as defined above,

(I)  $-C\equiv N$ ,

(j)  $-NO_2$ ,

15

where  $R_N$  is:

(1) -H,

(2)  $C_1-C_4$  alkyl,

(3)  $C_0-C_4-\phi$  where the  $-\phi$  substituent is optionally substituted with 1 or 2

(a) -F, -Cl, -Br, -I,

20

(b)  $-O-R_{N.1}$  where  $R_{N.1}$  is

-H,

$C_1-C_4$  alkyl,

$-\phi$ ,

(c)  $-CF_3$ ,

25

(d)  $-CO-NR_{N.2}R_{N.3}$  where  $R_{N.2}$  and  $R_{N.3}$  are -H and  $C_1-C_4$  alkyl, and where

$R_{N.2}$  and  $R_{N.3}$  are taken with the attached nitrogen atom to form a ring selected from the group consisting of 1-pyrrolidinyl, 1-piperazinyl and 1-morpholinyl,

(e)  $-NH-SO_2-R_{N.4}$  where  $R_{N.4}$  is -H and  $C_1-C_4$  alkyl,

(f)  $-NR_{N.2}R_{N.3}$  where  $R_{N.2}$  and  $R_{N.3}$  are as defined above,

30

(g)  $-NR_{N.4}-CO-R_{N.4}$  where  $R_{N.4}$  is as defined above,

(h)  $-SO_2-NR_{N.2}R_{N.3}$  where  $R_{N.2}$  and  $R_{N.3}$  are as defined above,

(I)  $-C\equiv N$ ,

(j)  $-NO_2$ ,

where  $R_X$  is:

- (1) -H
- (2) -F, -Cl, -Br, -I,
- (3) -O- $R_{X-1}$  where  $R_{X-1}$  is:
  - 5            -H,
  - C<sub>1</sub>-C<sub>4</sub> alkyl,
  - $\phi$ ,
  - (4) -CF<sub>3</sub>,
  - (5) -CO-NR<sub>X-2</sub>R<sub>X-3</sub> where R<sub>X-2</sub> and R<sub>X-3</sub> are as defined above,
  - 10        (6) -NH-SO<sub>2</sub>-R<sub>X-4</sub> where R<sub>X-4</sub> is as defined above,
  - (7) -NR<sub>X-2</sub>R<sub>X-3</sub> where R<sub>X-2</sub> and R<sub>X-3</sub> are as defined above,
  - (8) -NR<sub>X-4</sub>-CO-R<sub>X-4</sub> where R<sub>X-4</sub> is as defined above,
  - (9) -SO<sub>2</sub>-NR<sub>X-2</sub>R<sub>X-3</sub> where R<sub>X-2</sub> and R<sub>X-3</sub> are as defined above,
  - (10) -C $\equiv$ N,
  - 15        (11) -NO<sub>2</sub>;

where  $R_9$  is:

- (1) -H,
- (2) -F, -Cl,
- (3) C<sub>1</sub>-C<sub>4</sub> alkyl,
- 20        (4) C<sub>1</sub>-C<sub>3</sub> alkoxy,
- (5) -CF<sub>3</sub>,
- (6) C<sub>0</sub>-C<sub>4</sub>- $\phi$  where the  $\phi$  substituent is optionally substituted with 1 or 2
  - (a) -F, -Cl, -Br, -I,
  - (b) -O- $R_{9-1}$  where  $R_{9-1}$  is:
    - 25            -H,
    - C<sub>1</sub>-C<sub>4</sub> alkyl,
    - $\phi$ ,
    - (c) -CF<sub>3</sub>,
    - (d) -CO-NR<sub>9-2</sub>R<sub>9-3</sub> where R<sub>9-2</sub> and R<sub>9-3</sub> are -H and C<sub>1</sub>-C<sub>4</sub> alkyl, and where
    - 30        R<sub>9-2</sub> and R<sub>9-3</sub> are taken with the attached nitrogen atom to form a ring selected from the
    - group consisting of 1-pyrrolidinyl, 1-piperazinyl and 1-morpholinyl,
    - (e) -NH-SO<sub>2</sub>-R<sub>9-4</sub> where R<sub>9-4</sub> is -H and C<sub>1</sub>-C<sub>4</sub> alkyl,
    - (f) -NR<sub>9-2</sub>R<sub>9-3</sub> where R<sub>9-2</sub> and R<sub>9-3</sub> are as defined above,
    - (g) -NR<sub>9-4</sub>-CO-R<sub>9-4</sub> where R<sub>9-4</sub> is as defined above,

(h)  $-\text{SO}_2-\text{NR}_{9.2}\text{R}_{9.3}$  where  $\text{R}_{9.2}$  and  $\text{R}_{9.3}$  are as defined above,

(i)  $-\text{C}\equiv\text{N}$ ,

(j)  $-\text{NO}_2$

(7)  $-\text{OR}_{9.1}$  where  $\text{R}_{9.1}$  is as defined above,

5 (8)  $-\text{CO}-\text{NR}_{9.2}\text{R}_{9.3}$  where  $\text{R}_{9.2}$  and  $\text{R}_{9.3}$  are as defined above,

(9)  $-\text{NR}_{9.2}\text{R}_{9.3}$  where  $\text{R}_{9.2}$  and  $\text{R}_{9.3}$  are as defined above,

(10)  $-\text{NH}-\text{SO}_2-\text{R}_{9.4}$  where  $\text{R}_{9.4}$  is as defined above,

(11)  $-\text{NH}-\text{CO}_2-\text{R}_{9.2}$  where  $\text{R}_{9.2}$  is as defined above,

and pharmaceutically acceptable salts thereof.

10 Also disclosed are the thio ethers of formula (III), the amines of formula (IV), the hydrazines of formula (V), the compounds of formula (VII) and the protected 9-arylsulfones of formula (VIII) where PG is selected from the group consisting of  $\phi\text{-CH}_2-$ ,  $\phi\text{-CO-}$ ,  $\phi\text{-CH}_2\text{-CO}_2-$  and  $-\text{CO-O-C}(\text{CH}_3)_3$  and where  $\text{R}_9$  and  $\text{R}_x$  are as defined above.

Further disclosed is the use a 9-arylsulfone (XII) and pharmaceutically acceptable  
15 salts thereof for the manufacture of a medicament for use in treating a human who has a condition selected from the group consisting of anxiety, depression, schizophrenia, stress related disease, panic, a phobia, obsessive compulsive disorder, obesity, post-traumatic stress syndrome and who is in need of such treatment.

#### DETAILED DESCRIPTION OF THE INVENTION

20 The unsubstituted 9-arylsulfones (IX) and substituted 9-arylsulfones (X) are both prepared by means known to those skilled in the art. The term 9-arylsulfones (XII) includes both the unsubstituted 9-arylsulfones (IX), where  $\text{R}_3$  is  $-\text{H}$  and substituted 9-arylsulfones (X) where  $\text{R}_3$  is  $\neq$  to  $-\text{H}$ . The process of preparation can be viewed as being in two parts. The first part is the production of the appropriately substituted hydrazone (V), see CHART A.  
25 The second part is the coupling and reaction of the appropriately substituted hydrazone (V) with the 1-protected hexahydro-4H-azepine-4-one (VI) to give the intermediate (VII) and its transformation to the unsubstituted 9-arylsulfone (IX), see CHART B.

The appropriately substituted thiols (I) are either known to those skilled in the art or can be readily prepared from known starting materials by means well known to those skilled  
30 in the art. There can be either one or two  $\text{R}_9$  substituents and  $\text{R}_9$  includes  $-\text{H}$ ,  $-\text{F}$ ,  $-\text{Cl}$ ,  $\text{C}_1\text{-C}_3$  alkyl,  $\text{C}_1\text{-C}_3$  alkoxy and  $-\text{CF}_3$ ; it is preferred that  $\text{R}_9$  is  $-\text{H}$ ,  $-\text{F}$ ,  $-\text{Cl}$ ,  $\text{C}_1$  alkyl,  $\text{C}_1$  alkoxy, and  $-\text{CF}_3$  and when F- it is preferred that it be in the 4- or p-position. It is preferred that the  $\text{R}_9$  substituent be in either the 3- or 4-position.

The appropriately substituted thiol (I) is coupled with the appropriately substituted 4-chloro-1-nitrobenzene (II) by known means to produce the thioether (III). There can be either one or two  $R_x$  groups. If  $R_x$  is other than -H, it should be part of the 4-chloro-1-nitrobenzene (II) so that it will become part of the final unsubstituted 9-arylsulfone (IX) when it is formed.

5 It is most difficult to add the  $R_x$  substituent (other than -H) to the unsubstituted 9-arylsulfone (IX) once it is formed. Therefore, the  $R_x$  group should be part of the appropriately substituted 4-chloro-1-nitrobenzene (II) when it is reacted with the thiol (I).  $R_x$  includes of -H, -F and -Cl; it is preferred that  $R_x$  is -H. The thioether (III) is then oxidized with hydrogen peroxide (30%) followed by reduction with rhodium on carbon (5%), all of which is known to those

10 skilled in the art, to produce the amine (IV). The amine (IV) is then diazotized by (sodium) nitrite and (hydrochloric) acid followed by reduction with tin chloride/water to give the corresponding hydrazine (V).

The second part of the reaction, is well known to those skilled in the art, see US Patents 3,652,588, 3,676,558 and 3,839,357. The only difference between the process in

15 those patents and that here is the arylsulfone substituent at the 9-position. That substituent is already in place in the hydrazine (V) prior to the reaction of the 9-arylsulfone hydrazine (V) with the 1-protected hexahydro-4H-azepine-4-one (VI) to produce the correspondingly substituted intermediate (VII). Suitable protecting groups (PG) include  $\phi$ -CH<sub>2</sub>-,  $\phi$ -CO-,  $\phi$ -CH<sub>2</sub>-CO<sub>2</sub>- and -CO-O-C(CH<sub>3</sub>)<sub>3</sub>; it is preferred that the protecting group be  $\phi$ -CH<sub>2</sub>- or  $\phi$ -CO-.

20 The cyclization of the intermediate (VII) to the corresponding protected arylsulfone (VIII) and then the deprotection to the unsubstituted 9-arylsulfone (IX) all follow known methods. The protecting groups (PG) are readily removed by means well known to those skilled in the art. The unsubstituted 9-arylsulfone (IX) can then be substituted at the C3-position ( $R_3$ , ring nitrogen atom) as well as on the indole nitrogen ( $R_N$ ) as is known to those skilled in the art.

25 Alternatively, arylsulfone (VIII) can be alkylated with the desired  $R_N$ -X substituent to give the protected indole (XI) which then is deprotected to give the desired substituted 9-arylsulfone (X). Useful  $R_3$  groups include of -H and C<sub>1</sub>-C<sub>2</sub> alkyl; it is preferred that  $R_3$  be -H. Useful  $R_N$  groups include of -H and C<sub>1</sub>-C<sub>4</sub> alkyl; it is preferred that  $R_N$  is -H, C<sub>1</sub> alkyl and C<sub>2</sub> alkyl. The invention here is not the process chemistry but rather the novel products produced.

30 The preferred protecting group for the intermediates (VI), (VII) and (VIII) are benzyl and benzamide though other groups are operable as is known to those skilled in the art.

The 9-arylsulfones (XI) are amines, and as such form acid addition salts when reacted with acids of sufficient strength. Pharmaceutically acceptable salts include salts of

both inorganic and organic acids. The pharmaceutically acceptable salts are preferred over the corresponding free amines since they produce compounds which are more water soluble and more crystalline. The preferred pharmaceutically acceptable salts include salts of the following acids methanesulfonic, hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, benzoic, citric, tartaric, fumaric, maleic,  $\text{CH}_3-(\text{CH}_2)_n-\text{COOH}$  where n is 0 thru 4,  $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$  where n is as defined above. aa

The 9-arylsulfones (XI) of the present invention are useful to treat anxiety, depression, schizophrenia, stress related disease, panic, a phobia, obsessive compulsive disorder, obeisity, post-traumatic stress syndrome and other CNS disorders. It is preferred that the 9-aryl sulfones (XI) be used to treat anxiety for depression. To treat these diseases the 9-arylsulfones (XI) are administered orally, sublingually, transdermally or parenterally to provide a dosage of about 0.1 to about 50 mg/kg/day. It is preferred that the dosage range be from about 0.1 to about 10 mg/kg/day. The 9-arylsulfones (XI) can be administered in divided doses either two, three or four times daily. It is preferred that the 9-arylsulfones (XI) be administered orally.

The exact dosage and frequency of administration depends on the particular 9-arylsulfone(s) used, the particular disease being treated, the severity of the disease being treated, the age, weight, general physical condition of the particular patient, other medication the individual may be taking as is well known to those skilled in the art and can be more accurately determined by measuring the blood level or concentration of the 9-arylsulfone (XI) in the patient's blood and/or the patient's response to the particular condition being treated.

#### DEFINITIONS AND CONVENTIONS

The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims.

##### I. CONVENTIONS FOR FORMULAS AND DEFINITIONS OF VARIABLES

The chemical formulas representing various compounds or molecular fragments in the specification and claims may contain variable substituents in addition to expressly defined structural features. These variable substituents are identified by a letter or a letter followed by a numerical subscript, for example, " $\text{Z}_i$ " or " $\text{R}_i$ " where "i" is an integer. These variable substituents are either monovalent or bivalent, that is, they represent a group attached to the formula by one or two chemical bonds. For example, a group  $\text{Z}_i$  would represent a bivalent variable if attached to the formula  $\text{CH}_3-\text{C}(=\text{Z}_i)\text{H}$ . Groups  $\text{R}_i$  and  $\text{R}_j$  would represent monovalent variable substituents if attached to the formula  $\text{CH}_3-\text{CH}_2-$



-C(R<sub>i</sub>)(R<sub>j</sub>)-H. When chemical formulas are drawn in a linear fashion, such as those above, variable substituents contained in parentheses are bonded to the atom immediately to the left of the variable substituent enclosed in parenthesis. When two or more consecutive variable substituents are enclosed in parentheses, each of the consecutive variable substituents is bonded to the immediately preceding atom to the left which is not enclosed in parentheses. Thus, in the formula above, both R<sub>i</sub> and R<sub>j</sub> are bonded to the preceding carbon atom. Also, for any molecule with an established system of carbon atom numbering, such as steroids, these carbon atoms are designated as C<sub>i</sub>, where "i" is the integer corresponding to the carbon atom number. For example, C<sub>6</sub> represents the 6 position or carbon atom number in the steroid nucleus as traditionally designated by those skilled in the art of steroid chemistry. Likewise the term "R<sub>6</sub>" represents a variable substituent (either monovalent or bivalent) at the C<sub>6</sub> position.

Chemical formulas or portions thereof drawn in a linear fashion represent atoms in a linear chain. The symbol "-" in general represents a bond between two atoms in the chain. Thus CH<sub>3</sub>-O-CH<sub>2</sub>-CH(R<sub>i</sub>)-CH<sub>3</sub> represents a 2-substituted-1-methoxypropane compound. In a similar fashion, the symbol "=" represents a double bond, e.g., CH<sub>2</sub>=C(R<sub>i</sub>)-O-CH<sub>3</sub>, and the symbol "≡" represents a triple bond, e.g., HC≡C-CH(R<sub>i</sub>)-CH<sub>2</sub>-CH<sub>3</sub>. Carbonyl groups are represented in either one of two ways: -CO- or -C(=O)-, with the former being preferred for simplicity.

Chemical formulas of cyclic (ring) compounds or molecular fragments can be represented in a linear fashion. Thus, the compound 4-chloro-2-methylpyridine can be represented in linear fashion by N<sup>\*</sup>=C(CH<sub>3</sub>)-CH=CCl-CH=C<sup>\*</sup>H with the convention that the atoms marked with an asterisk (\*) are bonded to each other resulting in the formation of a ring. Likewise, the cyclic molecular fragment, 4-(ethyl)-1-piperazinyl can be represented by -N<sup>\*</sup>-(CH<sub>2</sub>)<sub>2</sub>-N(C<sub>2</sub>H<sub>5</sub>)-CH<sub>2</sub>-C<sup>\*</sup>H<sub>2</sub>.

A rigid cyclic (ring) structure for any compounds herein defines an orientation with respect to the plane of the ring for substituents attached to each carbon atom of the rigid cyclic compound. For saturated compounds which have two substituents attached to a carbon atom which is part of a cyclic system, -C(X<sub>1</sub>)(X<sub>2</sub>)- the two substituents may be in either an axial or equatorial position relative to the ring and may change between axial/equatorial. However, the position of the two substituents relative to the ring and each other remains fixed. While either substituent at times may lie in the plane of the ring (equatorial) rather than above or below the plane (axial), one substituent is always above the other. In chemical structural formulas depicting such compounds, a substituent (X<sub>1</sub>) which is

"below" another substituent ( $X_2$ ) will be identified as being in the alpha ( $\alpha$ ) configuration and is identified by a broken, dashed or dotted line attachment to the carbon atom, i.e., by the symbol "- - -" or "...". The corresponding substituent attached "above" ( $X_2$ ) the other ( $X_1$ ) is identified as being in the beta ( $\beta$ ) configuration and is indicated by an unbroken or  
 5 solid line attachment to the carbon atom.

When a variable substituent is bivalent, the valences may be taken together or separately or both in the definition of the variable. For example, a variable  $R_i$  attached to a carbon atom as  $-C(=R_i)-$  might be bivalent and be defined as oxo or keto (thus forming a carbonyl group  $(-CO-)$  or as two separately attached monovalent variable substituents  $\alpha-R_{i,j}$   
 10 and  $\beta-R_{i,k}$ . When a bivalent variable,  $R_i$ , is defined to consist of two monovalent variable substituents, the convention used to define the bivalent variable is of the form " $\alpha-R_{i,j}:\beta-R_{i,k}$ " or some variant thereof. In such a case both  $\alpha-R_{i,j}$  and  $\beta-R_{i,k}$  are attached to the carbon atom to give  $-C(\alpha-R_{i,j})(\beta-R_{i,k})-$ . For example, when the bivalent variable  $R_6$ ,  $-C(=R_6)-$  is defined to consist of two monovalent variable substituents, the two monovalent variable  
 15 substituents are  $\alpha-R_{6,1}:\beta-R_{6,2}$ , ...,  $\alpha-R_{6,9}:\beta-R_{6,10}$ , etc, giving  $-C(\alpha-R_{6,1})(\beta-R_{6,2})-$ , ...,  $-C(\alpha-R_{6,9})(\beta-R_{6,10})-$ , etc. Likewise, for the bivalent variable  $R_{11}$ ,  $-C(=R_{11})-$ , two monovalent variable substituents are  $\alpha-R_{11,1}:\beta-R_{11,2}$ . For a ring substituent for which separate  $\alpha$  and  $\beta$  orientations do not exist (e.g. due to the presence of a carbon carbon double bond in the ring), and for a substituent bonded to a carbon atom which is not part of a ring the above  
 20 convention is still used, but the  $\alpha$  and  $\beta$  designations are omitted.

Just as a bivalent variable may be defined as two separate monovalent variable substituents, two separate monovalent variable substituents may be defined to be taken together to form a bivalent variable. For example, in the formula  $-C_1(R_i)H-C_2(R_j)H-$  ( $C_1$  and  $C_2$  define arbitrarily a first and second carbon atom, respectively)  $R_i$  and  $R_j$  may be  
 25 defined to be taken together to form (1) a second bond between  $C_1$  and  $C_2$  or (2) a bivalent group such as oxa  $(-O-)$  and the formula thereby describes an epoxide. When  $R_i$  and  $R_j$  are taken together to form a more complex entity, such as the group  $-X-Y-$ , then the orientation of the entity is such that  $C_1$  in the above formula is bonded to  $X$  and  $C_2$  is bonded to  $Y$ . Thus, by convention the designation "...  $R_i$  and  $R_j$  are taken together to form  $-CH_2-CH_2-O-$   
 30  $CO-$  ..." means a lactone in which the carbonyl is bonded to  $C_2$ . However, when designated "...  $R_j$  and  $R_i$  are taken together to form  $-CO-O-CH_2-CH_2-$  the convention means a lactone in which the carbonyl is bonded to  $C_1$ .

The carbon atom content of variable substituents is indicated in one of two ways. The first method uses a prefix to the entire name of the variable such as " $C_1-C_4$ ", where

both "1" and "4" are integers representing the minimum and maximum number of carbon atoms in the variable. The prefix is separated from the variable by a space. For example, "C<sub>1</sub>-C<sub>4</sub> alkyl" represents alkyl of 1 through 4 carbon atoms, (including isomeric forms thereof unless an express indication to the contrary is given). Whenever this single prefix is given, the prefix indicates the entire carbon atom content of the variable being defined. Thus C<sub>2</sub>-C<sub>4</sub> alkoxycarbonyl describes a group CH<sub>3</sub>-(CH<sub>2</sub>)<sub>n</sub>-O-CO- where n is zero, one or two. By the second method the carbon atom content of only each portion of the definition is indicated separately by enclosing the "C<sub>i</sub>-C<sub>j</sub>" designation in parentheses and placing it immediately (no intervening space) before the portion of the definition being defined. By this optional convention (C<sub>1</sub>-C<sub>3</sub>)alkoxycarbonyl has the same meaning as C<sub>2</sub>-C<sub>4</sub> alkoxy-carbonyl because the "C<sub>1</sub>-C<sub>3</sub>" refers only to the carbon atom content of the alkoxy group. Similarly while both C<sub>2</sub>-C<sub>6</sub> alkoxyalkyl and (C<sub>1</sub>-C<sub>3</sub>)alkoxy(C<sub>1</sub>-C<sub>3</sub>)alkyl define alkoxyalkyl groups containing from 2 to 6 carbon atoms, the two definitions differ since the former definition allows either the alkoxy or alkyl portion alone to contain 4 or 5 carbon atoms while the latter definition limits either of these groups to 3 carbon atoms.

When the claims contain a fairly complex (cyclic) substituent, at the end of the phrase naming/designating that particular substituent will be a notation in (parentheses) which will correspond to the same name/designation in one of the CHARTS which will also set forth the chemical structural formula of that particular substituent.

## II. DEFINITIONS

All temperatures are in degrees Centigrade.

HPLC refers to high pressure liquid chromatography.

DMSO refers to dimethylsulfoxide.

DMF refers to dimethylformamide.

Saline refers to an aqueous saturated sodium chloride solution.

Chromatography (column and flash chromatography) refers to purification/separation of compounds expressed as (support, eluent). It is understood that the appropriate fractions are pooled and concentrated to give the desired compound(s).

IR refers to infrared spectroscopy.

NMR refers to nuclear (proton) magnetic resonance spectroscopy, chemical shifts are reported in ppm (d) downfield from tetramethylsilane.

-φ refers to phenyl (C<sub>6</sub>H<sub>5</sub>).

MS refers to mass spectrometry expressed as  $m/e$ ,  $m/z$  or mass/charge unit.  $[M + H]^+$  refers to the positive ion of a parent plus a hydrogen atom. EI refers to electron impact. CI refers to chemical ionization. FAB refers to fast atom bombardment.

HRMS refers to high resolution mass spectrometry.

5 Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

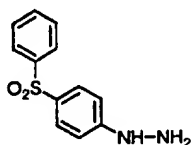
When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

10 When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

### EXAMPLES

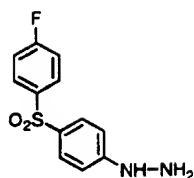
Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following  
15 detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

20 PREPARATION 1 1-[4-(Phenylsulfonyl)phenyl]hydrazine (V)



A mixture of 4-chlorophenyl phenyl sulfone (10.1 g, 40.0 mmol), hydrazine mono-hydrate (30 mL), and triethylamine (4 drops) in ethylene glycol (20 mL) is heated at 150° for 15 hr. Upon cooling, the mixture is diluted with H<sub>2</sub>O and filtered. The residual solid is  
25 washed with H<sub>2</sub>O until the washings are neutral (pH = 6). This material is then triturated with methylene chloride and dried under reduced pressure at 50° to give the title compound, IR (drift) 3282, 1586, 1514, 1306, 1291, 1158, 1145, 1104, 996, 813, 756, 730, 717, 688 and 678 cm<sup>-1</sup>; NMR (300 MHz, CDCl<sub>3</sub>) 7.70-7.85, 7.45-7.65, 6.79 and 4.22  $\delta$ ; MS (EI)  $m/z$  248 (M<sup>+</sup>), 125, 123, 108, 107, 90, 80, 77, 63 and 51.

30 PREPARATION 2 1-[4-[(4-Fluorophenyl)sulfonyl]phenyl]hydrazine (V)



Step I: 4-Fluorophenyl-4-nitrophenyl sulfide (III)

A mixture of 4-fluorothiophenol (I, 2.08 g, 19.5 mmol), 1-chloro-4-nitrobenzene (II, 3.39 g, 21.5 mmol), and potassium carbonate (5.40 g, 39.0 mmol) in acetonitrile (75 mL) is stirred at 20-25° under nitrogen for 16 hr. The mixture is diluted with H<sub>2</sub>O (100 mL) and extracted into methylene chloride (3 X 100 mL). The extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to provide a quantitative yield of the desired thioether, mp = 84-90°; NMR (300 MHz, CDCl<sub>3</sub>) 8.07, 7.45-7.60 and, 7.05-7.25 δ.

Step II: 4-[(4-Fluorophenyl)sulfonyl]phenylamine (IV)

A hot mixture (100°) of 4-fluorophenyl 4-nitrophenyl sulfide (III, Step I, 1.91 g, 7.66 mmol) in glacial acetic acid (50 mL) is treated with hydrogen peroxide (30%, 2.60 mL), followed 20 min later by a second portion of hydrogen peroxide (30%, 1.70 mL). The mixture continued to heat for an additional 30 min, and is then allowed to cool to 20-25°. The mixture is concentrated to near dryness and filtered, rinsing the solid with H<sub>2</sub>O. The solid is dried in a vacuum oven at 50° to give the intermediate sulfone, IR (drift) 1590, 1534, 1356, 1307, 1294, 1242, 1166, 1156, 1109, 1101, 858, 839, 742, 687 and 665 cm<sup>-1</sup>; NMR (300 MHz, CDCl<sub>3</sub>) 8.35, 8.12, 7.95-8.05 and 7.15-7.30 δ; MS (EI) *m/z* 281 (M<sup>+</sup>), 159, 143, 111, 95, 95, 83, 76, 74 and 51.

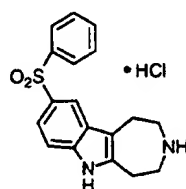
A mixture of 4-fluorophenyl 4-nitrophenyl sulfone (1.89 g, 6.72 mmol) in methanol (80 mL) is treated with Rhodium on carbon (5%, 95 mg) and hydrogenated at 20 psi for 24 hr. The mixture is filtered, rinsing with methylene chloride (2 X 100 mL) and methanol (100 mL). The filtrate is concentrated to near dryness and refiltered, rinsing with minimal methanol. The solid is dried in the vacuum oven at 50° to give the desired amine, mp = 204-205°; IR (drift) 3473, 3373, 1638, 1592, 1489, 1303, 1294, 1285, 1231, 1159, 1144, 1107, 834, 713 and 689 cm<sup>-1</sup>; NMR (300 MHz, CDCl<sub>3</sub>) 7.80-7.95, 7.60-7.75, 7.13, 6.60-6.75 and 4.17 δ; MS (EI) *m/z* 251 (M<sup>+</sup>), 140, 108, 95, 92, 80, 65, 65, 63 and 51.

Step III: 1-[4-[(4-fluorophenyl)sulfonyl]phenyl]hydrazine (V)

A mixture of 4-[(4-fluorophenyl)sulfonyl]phenylamine (IV, Step II, 3.10 g, 12.3 mmol) in concentrated hydrochloric acid (30 mL) at 0° is treated with sodium nitrite (934

mg, 13.5 mmol) in H<sub>2</sub>O (15 mL). After 30 min, the mixture is treated with stannous chloride (5.57 g, 24.7 mmol) in concentrated hydrochloric acid (15 mL). The mixture is stirred at 0° for 1 hr, and then at 20-25° for 1 hr. The precipitate is collected and slurried in H<sub>2</sub>O. The mixture is made basic (sodium hydroxide, 50%) and the solid isolated. The material is partitioned between methylene chloride and saline. The organic layer is dried, filtered, and concentrated under reduced pressure to give the title compound, NMR (300 MHz, CDCl<sub>3</sub>) 7.85-7.95, 7.74, 7.13, 6.85, 5.64 and 3.65 δ.

EXAMPLE 1 9-(Phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (IX)



10

Step I: 1-Benzyl-4-azepanone N-[4-(phenylsulfonyl)phenyl]hydrazone (VII)

A mixture of 1-[4-(phenylsulfonyl)phenyl]hydrazine (V, PREPARATION 1, 7.06 g, 28.4 mmol) and 4-benzylazepanone (VI, 5.78 g, 28.4 mmol) in ethanol (130 mL) is treated with glacial acetic acid (8 drops) and heated at reflux for 1 hr. Upon cooling, the precipitate is collected, washed with ethanol and dried in the vacuum oven at 50° to give the desired compound, mp = 142-146°. The filtrate is concentrated and purified via flash chromatography (ethyl acetate/heptane; 65/35) to provide additional product as two regioisomers. Analytical data for one isomer: IR (drift) 1593, 1511, 1323, 1301, 1261, 1148, 1106, 1069, 833, 758, 748, 735, 709, 689 and 600 cm<sup>-1</sup>; NMR (300 MHz, CDCl<sub>3</sub>) 7.85-7.95, 7.77, 7.40-7.65, 7.15-7.35, 7.06, 3.65, 2.65-2.85, 2.55-2.65, 2.35-2.45 and, 1.70-1.85; MS (EI) *m/z* 433 (M<sup>+</sup>), 186, 120, 108, 97, 96, 91, 82, 77, 65 and 51. Analytical data for the slower eluting isomer: IR (drift) 1593, 1509, 1324, 1296, 1285, 1264, 1148, 1106, 1085, 1069, 834, 735, 710, 688 and 605 cm<sup>-1</sup>; NMR (300 MHz, CDCl<sub>3</sub>) 7.85-7.95, 7.70-7.85, 7.35-7.55, 7.15-7.35, 7.06, 3.60, 2.55-2.75, 3.32-2.45 and 1.85-2.00; MS (EI) *m/z* 433 (M<sup>+</sup>), 187, 186, 120, 108, 97, 91, 82, 77, 65 and 51.

25

Step II: 3-Benzyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (VIII)

A mixture of 1-benzyl-4-azepanone N-[4-(phenylsulfonyl)phenyl]hydrazone (VII, Step I, 3.41 g, 7.86 mmol) and polyphosphoric acid (4.78 g) in *o*-xylene (550 mL) is heated at 100° under nitrogen for 3 hr. Upon cooling, the xylene is decanted and the residual material partitioned between methylene chloride/methanol and sodium hydroxide (0.5 M).

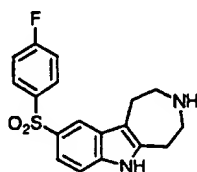
30

The phases are separated and the aqueous layer is further extracted with more methylene chloride/methanol (2 X). The organic phases are combined and dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give an oil. The oil is purified by flash chromatography (Biotage 40M; ethyl acetate/heptane, 7/3) to give the  
 5 desired indole, mp = 86-88°, dec; IR (drift) 3343, 2910, 1475, 1449, 1337, 1301, 1146, 1131, 1090, 748, 731, 719, 698, 688 and 627 cm<sup>-1</sup>; NMR (300 MHz, CDCl<sub>3</sub>) 8.10-8.20, 8.06, 7.96, 7.66, 7.25-7.55, 3.85 and 2.90-3.05 δ; MS (EI) *m/z* 416 (M<sup>+</sup>), 296, 154, 146, 134, 134, 132, 120, 91 and 65.

Step III: 9-(Phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (IX)

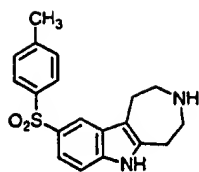
10 A mixture of 3-benzyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (VIII, Step II, 453 mg, 1.09 mmol) in methanol (50 mL) is treated with palladium hydroxide (118 mg) and hydrogenated at 30 psi for 5 days. The mixture is filtered, rinsing with methanol and methylene chloride, and the filtrate concentrated under reduced pressure to give an amorphous solid. The material is purified by flash chromatography (Biotage  
 15 40M; methanol/methylene chloride, 5/95; methanol/ methylene chloride /ammonium hydroxide, 20/79/1) to give the title compound. Analytical data for the hydrochloride salt, mp = 290-291.5°; IR (drift) 3382, 2751, 2698, 2689, 2646, 2438, 1297, 1150, 1131, 1095, 801, 759, 722, 684 and 616 cm<sup>-1</sup>; NMR (300 MHz, DMSO-*d*<sub>6</sub>) 11.65, 7.35, 8.05-8.15, 7.85-7.95, 7.40-7.65, 3.20-3.40 and 3.10-3.25 δ; MS (EI) *m/z* 326 (M<sup>+</sup>), 298, 297, 286, 285,  
 20 284, 143 and 77; HRMS (FAB) calculated for C<sub>18</sub>H<sub>19</sub>N<sub>2</sub>O<sub>2</sub>S = 327.1167, found 327.1165.

EXAMPLE 2 9-[(4-Fluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (IX)



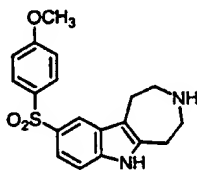
Following the general procedure of EXAMPLE 1 (Steps I-III) and making non-  
 25 critical variations, 1-[4-[(4-fluorophenyl)sulfonyl]phenyl]hydrazine (V, PREPARATION 2) is converted to the title compound, mp = 168°, dec.; IR (drift) 2923, 1590, 1491, 1475, 1336, 1308, 1287, 1236, 1147, 1131, 1089, 837, 816, 749 and 683 cm<sup>-1</sup>; NMR (300 MHz, CDCl<sub>3</sub>) 8.05-8.15, 8.05, 7.90-8.00, 7.55-7.65, 7.30-7.35, 7.12, 3.05-3.15 and 2.90-3.00 δ; HRMS (FAB) calculated for C<sub>18</sub>H<sub>18</sub>FN<sub>2</sub>O<sub>2</sub>S = 345.1073, found 345.1087.

30 EXAMPLE 3 9-[(4-Methylphenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (IX)



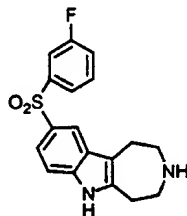
Following the general procedure of EXAMPLE 1 (Steps I-III) and making non-critical variations, 1-[4-[(4-methylphenyl)sulfonyl]phenyl]hydrazine (V, PREPARATION 2) is converted to the title compound, mp = 125°, dec; IR (drift) 3027, 2921, 2830, 1475, 1453, 1336, 1298, 1287, 1150, 1130, 1090, 812, 747, 682 and 658 cm<sup>-1</sup>; NMR (300 MHz, CDCl<sub>3</sub>) 8.12, 7.83, 7.55-7.65, 7.20-7.35, 3.05-3.20, 2.90-3.05 and 2.36 δ; MS (EI) *m/z* 340 (M<sup>+</sup>), 311, 298, 154, 144, 143, 115, 91, 91 and 65; HRMS (FAB) calculated for C<sub>19</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub>S = 341.1324, found 341.1311.

EXAMPLE 4 9-[(4-Methoxyphenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (IX)



Following the general procedure of EXAMPLE 1, and making non-critical variations, 1-[4-[(4-methylphenyl)sulfonyl]phenyl]hydrazine (V, PREPARATION 2) is converted to the title compound, mp = 139°, dec.; IR (drift) 2927, 2837, 1593, 1496, 1335, 1312, 1293, 1260, 1142, 1130, 1092, 834, 802, 748 and 683 cm<sup>-1</sup>; NMR (300 MHz, DMSO-*d*<sub>6</sub>) 11.30, 7.90-8.00, 7.75-7.85, 7.40-7.50, 7.30-7.40, 7.00-7.10, 3.77 and 2.75-3.05; MS (EI) *m/z* 356 (M<sup>+</sup>), 327, 314, 155, 154, 143, 143, 115, 77 and 57; HRMS (FAB) calculated for C<sub>19</sub>H<sub>21</sub>N<sub>2</sub>O<sub>3</sub>S = 357.1273, found 357.1275.

EXAMPLE 5 9-[(3-Fluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (IX)

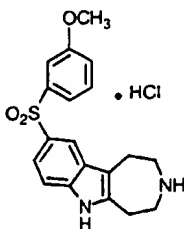


Following the general procedure of EXAMPLE 1, and making non-critical variations, 1-[4-[(3-fluorophenyl)sulfonyl]phenyl]hydrazine (V, PREPARATION 2) is



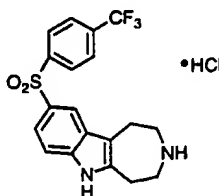
converted to the title compound, mp = 153-156°: IR (drift) 2926, 2867, 2855, 1474, 1311, 1296, 1225, 1151, 1129, 1082, 773, 742, 698, 677 and 629  $\text{cm}^{-1}$ ; NMR (300 MHz, DMSO- $d_6$ ) 11.37, 8.00-8.10, 7.70-7.80, 7.30-7.75 and 2.75-2.95  $\delta$ ; MS (EI)  $m/z$  344 ( $M^+$ ), 315, 302, 154, 144, 143, 128, 128, 115 and 73; HRMS (FAB) calculated for  $C_{18}H_{18}FN_2O_2S$  = 345.1073, found 345.1075.

EXAMPLE 6 9-[(3-Methoxyphenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole hydrochloride (IX)



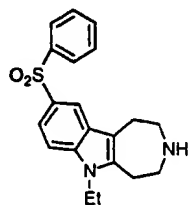
Following the general procedure of EXAMPLE 1, and making non-critical variations, 1-[4-[(3-methoxyphenyl)sulfonyl]phenyl]hydrazine (V, PREPARATION 2) is converted to the title compound, mp = 232-235°, dec.; IR (drift) 2976, 2963, 2832, 2805, 2770, 2739, 1475, 1303, 1248, 1151, 1141, 746, 694, 682 and 629  $\text{cm}^{-1}$ ; NMR (300 MHz, DMSO- $d_6$ ) 11.63, 9.31, 8.10-8.15, 7.35-7.60, 7.10-7.20, 3.79, 3.20-3.40 and 3.05-3.40  $\delta$ ; MS (EI)  $m/z$  356 ( $M^+$ ), 327, 314, 107, 74, 73, 59, 57, 57 and 56; MS (FAB)  $m/z$  357 ( $MH^+$ ), 356, 328, 177, 155, 121, 103, 89; HRMS (FAB) calculated for  $C_{19}H_{21}N_2O_3S$  = 357.1273, found 357.1277.

EXAMPLE 7 9-[(4-Trifluoromethylphenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole hydrochloride (IX)



Following the general procedure of EXAMPLE 1, and making non-critical variations, 1-[4-[(4-trifluoromethylphenyl)sulfonyl]phenyl]hydrazine (V, PREPARATION 2) is converted to the title compound, mp = 278-279°, dec.; IR (drift) 2773, 2756, 2732, 1321, 1306, 1178, 1156, 1133, 1122, 1108, 1061, 844, 716, 623 and 618  $\text{cm}^{-1}$ ; NMR (300 MHz, DMSO- $d_6$ ) 8.05-8.20, 7.90-8.00, 7.55-7.45, 7.45-7.55 and 3.05-3.40  $\delta$ ; MS (EI)  $m/z$  394 ( $M^+$ ), 365, 352, 154, 143, 73, 71, 59, 58 and 57.

**EXAMPLE 8**      **6-Ethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (IX)**



Step I: 3-Benzyl-6-ethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole

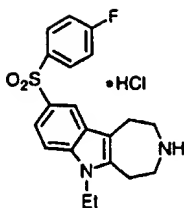
5      A 0° mixture of 3-benzyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (EXAMPLE 1, Step II, 301 mg, 0.723 mmol) in dry DMF (5 mL) is treated with sodium hydride (60% in oil, 32 mg, 0.795 mmol), and allowed to warm to 20-25° over 1.5 hr. The mixture is then cooled (0°), treated with iodoethane (64 µL, 0.795 mmol) and allowed to slowly warm to 20-25° under nitrogen over 72 hr. The resultant mixture is  
10 diluted with ethyl acetate (50 mL) and washed with H<sub>2</sub>O (3 X 25 mL) and saline (25 mL). The organic layer is dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give a solid. The solid is purified via chromatography (20 g SG; ethyl acetate/heptane, 65/35) to give the indole as a solid, mp = 188-191°; IR (drift) 1477, 1373, 1300, 1289, 1157, 1148, 1094, 766, 756, 738, 728, 701, 694, 645 and 621 cm<sup>-1</sup>; NMR  
15 (300 MHz, CDCl<sub>3</sub>) 8.10-8.20, 7.90-8.05, 7.65-7.75, 7.20-7.50, 4.11, 3.82, 2.85-3.05 and 1.27 δ; MS (EI) *m/z* 444 (M<sup>+</sup>), 326, 324, 312, 167, 154, 132, 118, 96, 91 and 64.

Step II: 6-Ethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (X)

A mixture of 3-benzyl-6-ethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (Step I, 107 mg, 0.241 mmol) in methanol (20 mL, 1 drop  
20 concentrated hydrochloric acid) is treated with palladium on carbon (10%, 32 mg) and hydrogenated at 25 psi for 48 hr. The resulting mixture is filtered, rinsing with methanol and methylene chloride, and the filtrate is concentrated to a solid. The solid is purified via chromatography (10 g SG; methanol/methylene chloride /ammonium hydroxide, 20/79/1) to give the title compound, mp = 224°, dec.; IR (drift) 2982, 2935, 2743, 1473, 1449, 1312,  
25 1300, 1151, 1091, 819, 768, 728, 691, 647 and 623 cm<sup>-1</sup>; NMR (300 MHz, DMSO-*d*<sub>6</sub>) 8.09, 7.85-7.95, 7.45-7.65, 4.20, 2.95-3.25 and 1.15 δ; MS (EI) *m/z* 354 (M<sup>+</sup>), 312, 170, 167, 153, 143, 114, 78, 76 and 51; HRMS (FAB) calculated for C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub>S = 355.1480, found 355.1488.

**EXAMPLE 9**      **6-Ethyl-9-[(4-fluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole hydrochloride (IX)**

30

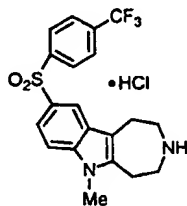


Following the general procedure of EXAMPLE 8, and making non-critical variations, 3-benzyl-9-[(4-fluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (EXAMPLE 2) is converted to the title compound, mp = 227-233°, dec.; IR (drift) 2972, 2834, 2755, 2713, 2679, 1589, 1490, 1471, 1312, 1293, 1223, 1148, 1094, 715 and 693 cm<sup>-1</sup>; MS (EI) *m/z* 372 (M<sup>+</sup>), 331, 330, 171, 171, 154, 143, 143, 91 and 57; NMR (300 MHz, DMSO-*d*<sub>6</sub>) 9.30, 8.18, 8.02, 7.55-7.70, 7.41, 4.24, 3.10-3.40 and 1.19 δ; MS (FAB) *m/z* 373 (MH<sup>+</sup>), 372, 371, 344 and 330; HRMS (FAB) calculated for C<sub>20</sub>H<sub>22</sub>FN<sub>2</sub>O<sub>2</sub>S = 373.1386, found 373.1371.

EXAMPLE 10      6-Methyl-9-[(4-fluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole hydrochloride (IX)

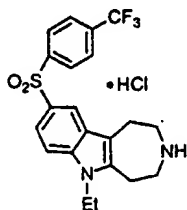
Following the general procedure of EXAMPLE 8, and making non-critical variations, 3-benzyl-9-[(4-fluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (EXAMPLE 2) is converted to the title compound, mp >300°; IR (drift) 2775, 1589, 1489, 1310, 1288, 1237, 1149, 1091, 841, 836, 805, 718, 667, 639 and 605 cm<sup>-1</sup>; NMR (300 MHz, DMSO-*d*<sub>6</sub>) 9.51, 8.17, 8.01, 7.63, 7.41, 3.72 and 3.10-3.45 δ.

EXAMPLE 11      6-Methyl-9-[(4-trifluoromethylphenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole hydrochloride (IX)



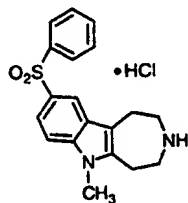
Following the general procedure of EXAMPLE 8, and making non-critical variations, 3-benzyl-9-[(4-trifluoromethylphenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (EXAMPLE 7) is converted to the title compound, mp = 286°, dec.; IR (drift) 2740, 2716, 1321, 1309, 1187, 1172, 1155, 1132, 1109, 1098, 1063, 845, 719, 648 and 625 cm<sup>-1</sup>; NMR (300 MHz, DMSO-*d*<sub>6</sub>) 9.31, 8.19, 8.13, 7.93, 7.64, 3.71 and 3.10-3.40 δ.

EXAMPLE 12      6-Ethyl-9-[(4-trifluoromethylphenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole hydrochloride (IX)



Following the general procedure of EXAMPLE 8, and making non-critical variations, 3-benzyl-9-[(4-trifluoromethylphenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (EXAMPLE 7) is converted to the title compound, mp = 170-179°, dec.; IR (drift) 2762, 1326, 1302, 1294, 1190, 1184, 1171, 1153, 1138, 1109, 1095, 1064, 830, 716 and 618  $\text{cm}^{-1}$ ; NMR (300 MHz, DMSO- $d_6$ ) 9.40, 8.20, 8.14, 7.93, 7.65, 4.15-4.30, 3.10-3.45 and 1.10-1.20  $\delta$ .

EXAMPLE 13      6-Methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole hydrochloride (IX)



Step I: 1-Benzoyl-4-azepanone N-[4-(phenylsulfonyl)phenyl]hydrazone

A mixture of 1-[4-(phenylsulfonyl)phenyl]hydrazine (2.05 g, 8.26 mmol) and 4-benzoylazepanone (1.97 g, 9.09 mmol) in ethanol (40 mL) is treated with glacial acetic acid (8 drops) and heated at reflux for 1 hr. Upon cooling, the precipitate is collected, washed with ethanol and dried in the vacuum oven (50°) to give the desired hydrazone, mp = 202-204°.

Step II: 3-Benzoyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole

A mixture of 1-benzoyl-4-azepanone N-[4-(phenylsulfonyl)phenyl]hydrazone (Step I, 2.00 g, 4.47 mmol) in dichloroethane/phosphoric acid 84% (1/1, 40 mL) is heated at reflux for 16 hr. Upon cooling, the product is diluted with saline and extracted into methylene chloride (3 X). The extracts are dried, filtered, and concentrated under reduced pressure to give a solid. The solid is purified via silica gel chromatography (Biotage 40M; ethyl acetate/heptane, 75/25) to give the desired indole.

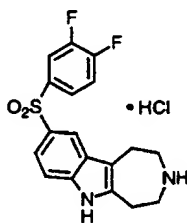
Step III: 3-Benzoyl-6-methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole

A 0° mixture of 3-benzoyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (Step II, 1.61 g, 3.74 mmol) in dry DMF (18 mL) is treated with sodium hydride (60% in oil, 165 mg, 4.11 mmol). After 30 min, the mixture is treated with iodomethane (256  $\mu$ L, 4.11 mmol) and allowed to slowly warm to 20-25° under nitrogen over 16 hr. The resultant mixture is diluted with H<sub>2</sub>O and filtered. The residual solid is triturated with refluxing methanol, isolated, and dried in the vacuum oven at 50° to give the desired indole, mp = 254-255°.

Step IV: 6-Methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole hydrochloride

A mixture of 3-benzoyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (Step III, 1.25 g, 2.81 mmol) and potassium hydroxide (1.58 g, 28.1 mmol) in ethylene glycol (30 mL) is heated at 130° under nitrogen for 92 hr. Upon cooling, the mixture is diluted with H<sub>2</sub>O and extracted into ethyl acetate (3 x). The combined extracts are washed with H<sub>2</sub>O (2 x) and saline, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give a solid. The solid is dissolved in hot methylene chloride/methanol and treated with methanolic hydrochloric acid. The resultant mixture is concentrated and crystallized from ethyl acetate/methanol to give the title compound, mp > 300°; IR (drift) 2820, 2792, 2747, 2717, 2704, 2665, 2651, 1299, 1147, 1096, 803, 729, 687, 643 and 621 cm<sup>-1</sup>; NMR (300 MHz, DMSO-*d*<sub>6</sub>) 9.41, 8.13, 7.85-7.95, 7.50-7.65, 3.70 and 3.10-3.40  $\delta$ ; MS (EI) *m/z* 340 (M<sup>+</sup>), 298, 157, 156, 128, 78, 74, 73, 58 and 57; HRMS (FAB) calculated for C<sub>19</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub>S = 341.1324, found = 341.1319.

EXAMPLE 14 9-[(3,4-Difluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (IX)

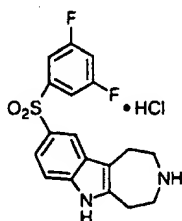


Following the general procedure of EXAMPLE 1 (steps I-III) and making non-critical variations, 1-[4-[(3,4-difluorophenyl)sulfonyl]phenyl]hydrazine (V,

PREPARATION 2) is converted to the title compound, mp = 320°, dec; IR (drift) 2732, 1507, 1310, 1293, 1277, 1147, 1128, 1116, 1072, 800, 751, 686, 627, 622 and 610 cm<sup>-1</sup>;

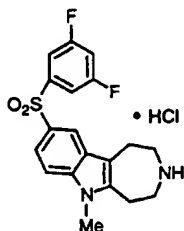
NMR (300 MHz, DMSO- $d_6$ )  $\delta$  11.75, 9.50, 8.10-8.20, 7.75-7.85, 7.55-7.70, 7.40-7.50, 3.25-3.40 and 3.10-3.25; OAMS (supporting ions at): ESI+ 363.1, ESI- 361.0.

EXAMPLE 15 9-[(3,5-Difluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (IX)



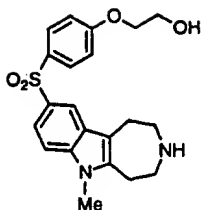
5 Following the general procedure of EXAMPLE 1 (steps I-III) and making non-critical variations, 1-[4-[(3,5-difluorophenyl)sulfonyl]phenyl]hydrazine (V, PREPARATION 2) is converted to the title compound, mp = 313-315°, dec; IR (drift) 3256, 1606, 1591, 1307, 1285, 1269, 1153, 1138, 1122, 983, 850, 795, 678, 666 and 618  
10  $\text{cm}^{-1}$ ; NMR (300 MHz, DMSO- $d_6$ )  $\delta$  11.70, 9.35, 8.15-8.25, 7.40-7.85 and 3.10-3.40; MS (EI)  $m/z$  362 ( $M^+$ ), 333, 320, 154, 142, 127, 115, 113, 92 and 63.

EXAMPLE 16 9-[(3,5-Difluorophenyl)sulfonyl]-6-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole hydrochloride (IX)



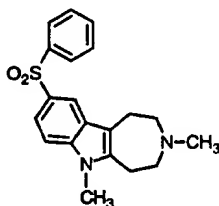
15 Following the general procedure of EXAMPLE 13 (steps I-IV) and making non-critical variations, 1-[4-[(3,5-difluorophenyl)sulfonyl]phenyl]hydrazine (V, PREPARATION 2) (EXAMPLE 2) is converted to the title compound, mp = 337-340°, dec; IR (drift) 2767, 2750, 1603, 1437, 1308, 1295, 1144, 1129, 988, 807, 709, 681, 675,  
20 650 and 627  $\text{cm}^{-1}$ ; NMR (300 MHz, DMSO- $d_6$ )  $\delta$  9.35, 8.20-8.30, 7.60-7.80, 3.71 and 3.15-3.45; MS (EI)  $m/z$  376 ( $M^+$ ), 334, 334, 156, 114, 113, 64, 63, 57, 52 and 51; HRMS (FAB) calculated for  $\text{C}_{19}\text{H}_{19}\text{F}_2\text{N}_2\text{O}_2\text{S}$  = 377.1135, found = 377.1125.

EXAMPLE 17 9-[(4-(2-Hydroxyethoxy)phenyl)sulfonyl]-6-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole hydrochloride (IX)



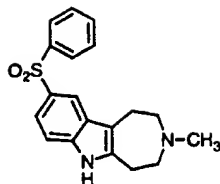
Following the general procedure of EXAMPLE 13 (steps I-IV) and making non-critical variations, 1-[4-[(4-fluorophenyl)sulfonyl]phenyl]hydrazine (V, PREPARATION 2) is converted to the title compound, mp = 285-287°, dec; IR (drift) 2957, 2835, 2811, 2760, 1592, 1492, 1458, 1309, 1293, 1261, 1142, 1092, 721, 637 and 618 cm<sup>-1</sup>; NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 9.43, 8.09, 7.81, 7.57, 7.06, 4.85-4.95, 3.95-4.05, 3.69 and 3.00-3.45; MS (EI) *m/z* 400 (M<sup>+</sup>), 86, 84, 77, 73, 72, 71, 58, 57, 56 and 51; HRMS (FAB) calculated for C<sub>21</sub>H<sub>25</sub>N<sub>2</sub>O<sub>4</sub>S = 401.1535, found = 401.1540.

EXAMPLE 18 3,6-Dimethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (X)



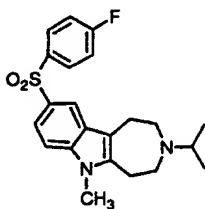
A mixture of 6-methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (EXAMPLE 13, 341 mg, 1.00 mmol) in acetonitrile (5 mL) is treated with formaldehyde (37%, 0.400 mL, 5.00 mmol), sodium cyanoborohydride (101 mg, 1.60 mmol) and glacial acetic acid (1 drop). After 5 hr, the mixture is diluted with ethyl acetate and then washed with water and saline. The organic layer is dried, filtered, and concentrated. The concentrate is dissolved in methylene chloride/methanol and treated with methanolic hydrochloric acid. The solvent is then removed and the residual solid crystallized from hot ethyl acetate/methanol to give the title compound, mp = 283-286°; IR (drift) 2523, 2477, 2453, 2428, 1479, 1311, 1304, 1283, 1150, 1094, 756, 730, 694, 644 and 623 cm<sup>-1</sup>; NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 11.00, 8.16, 7.85-7.95, 7.50-7.65, 3.70, 3.15-3.45 and 2.89; MS (FAB) *m/z* 355 (MH<sup>+</sup>), 354, 353, 58 and 44; HRMS (FAB) calculated for C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub>S = 355.1480, found = 355.1488.

EXAMPLE 19 3-Methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (X)



Following the general procedure of EXAMPLE 18, and making non-critical variations, 9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (EXAMPLE 1) is converted to the title compound, mp = 150°, dec; IR (drift) 2623, 1474, 1447, 1338, 1301, 1173, 1152, 1129, 1090, 755, 741, 719, 689, 673 and 615 cm<sup>-1</sup>; NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 11.68, 8.14, 7.85-7.95, 7.40-7.65, 3.10-3.45 and 2.88; MS (EI) *m/z* 340 (M<sup>+</sup>), 296, 77, 74, 73, 72, 71, 58, 57, 56 and 51; HRMS (FAB) calculated for C<sub>19</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub>S = 341.1324, found = 341.1331.

EXAMPLE 20 9-[(4-fluorophenyl)sulfonyl]-3-isopropyl-6-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (X)



Following the general procedure of EXAMPLE 18, and making non-critical variations, 6-methyl-9-[(4-fluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (EXAMPLE 10) ) is converted to the title compound, mp = 282-283°, dec; IR (drift) 2479, 2437, 1589, 1490, 1310, 1284, 1239, 1161, 1144, 1092, 838, 809, 718, 677 and 667 cm<sup>-1</sup>; NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 10.60, 8.17, 7.99, 7.62, 7.39, 3.71, 3.10-3.75 and 1.31; MS (EI) *m/z* 400 (M<sup>+</sup>), 385, 328, 315, 169, 167, 127, 85, 71, 70 and 56; HRMS (FAB) calculated for C<sub>22</sub>H<sub>26</sub>FN<sub>2</sub>O<sub>2</sub>S = 401.1699, found = 401.1709.

#### EXAMPLES 21-44

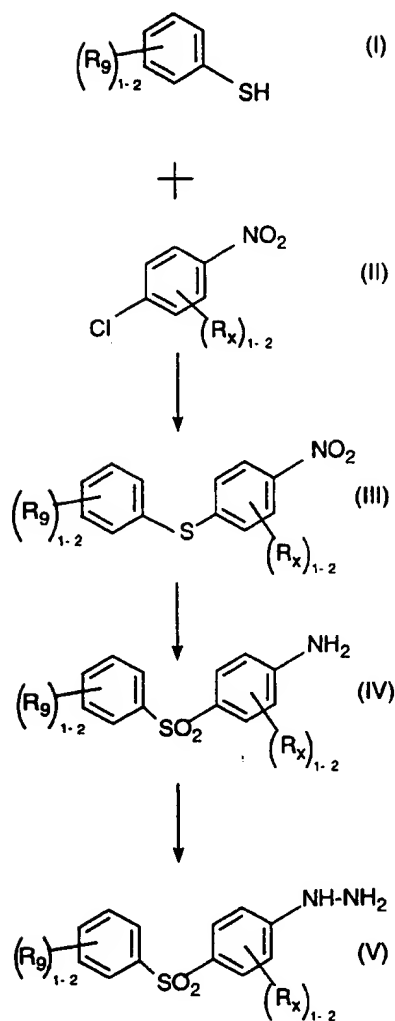
Following the general procedure of the above EXAMPLEs, making non-critical variations and starting with the corresponding appropriate starting materials, the following compounds are obtained:

21. 1-Methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole
22. 2-Methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole
23. 4-Methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole
24. 5-Methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole
25. 9-[(4-Fluorophenyl)sulfonyl]-1-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole



26. 9-[(4-Fluorophenyl)sulfonyl]-2-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole  
27. 9-[(4-Fluorophenyl)sulfonyl]-4-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole  
28. 9-[(4-Fluorophenyl)sulfonyl]-5-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole  
29. 1,6-Dimethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole  
5 30. 2,6-Dimethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole  
31. 4,6-Dimethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole  
32. 5,6-Dimethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole  
33. 9-[(4-Fluorophenyl)sulfonyl]-1,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole  
34. 9-[(4-Fluorophenyl)sulfonyl]-2,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole  
10 35. 9-[(4-Fluorophenyl)sulfonyl]-4,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole  
36. 9-[(4-Fluorophenyl)sulfonyl]-5,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole  
37. 9-[(3,5-Difluorophenyl)sulfonyl]-1-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole  
38. 9-[(3,5-Difluorophenyl)sulfonyl]-2-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole  
39. 9-[(3,5-Difluorophenyl)sulfonyl]-4-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole  
15 40. 9-[(3,5-Difluorophenyl)sulfonyl]-5-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole  
41. 9-[(3,5-Difluorophenyl)sulfonyl]-1,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole  
42. 9-[(3,5-Difluorophenyl)sulfonyl]-2,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole  
20 43. 9-[(3,5-Difluorophenyl)sulfonyl]-4,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole  
44. 9-[(3,5-Difluorophenyl)sulfonyl]-5,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole

## CHART A



## CHART B

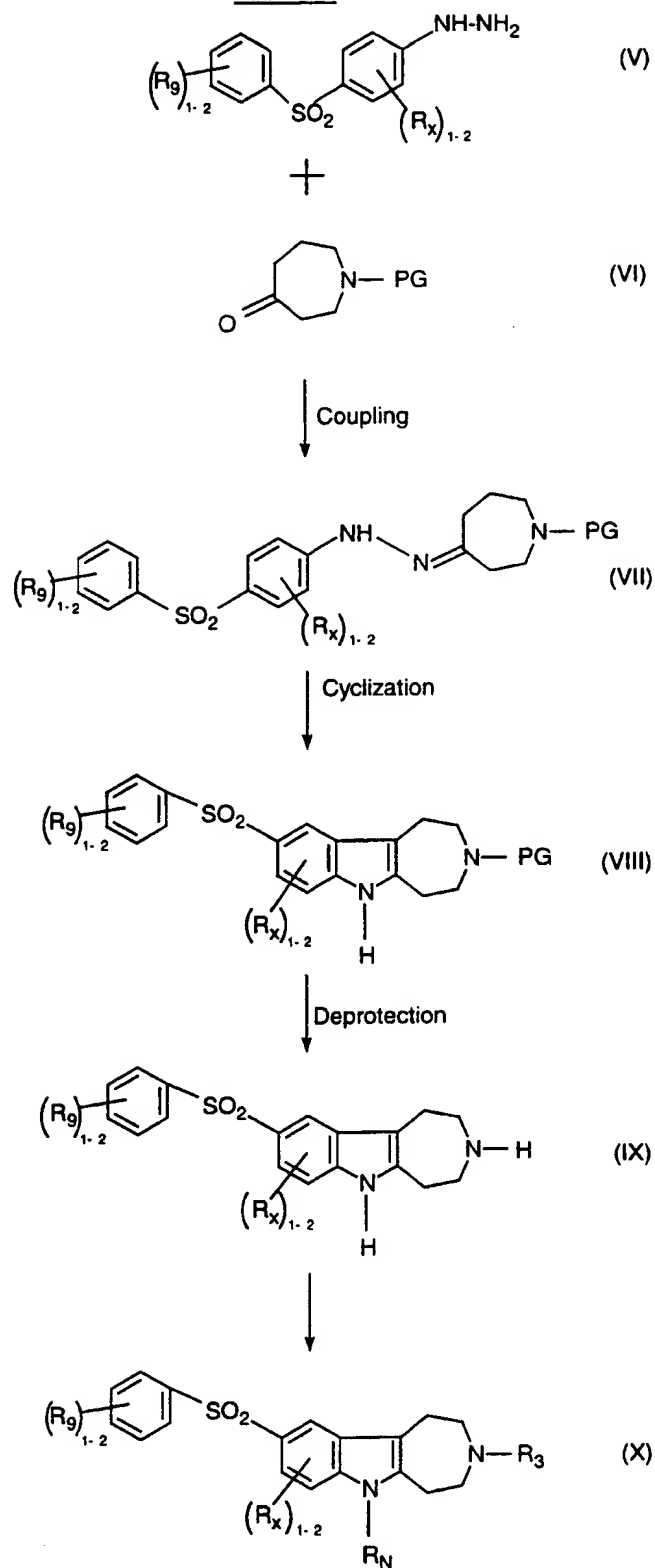
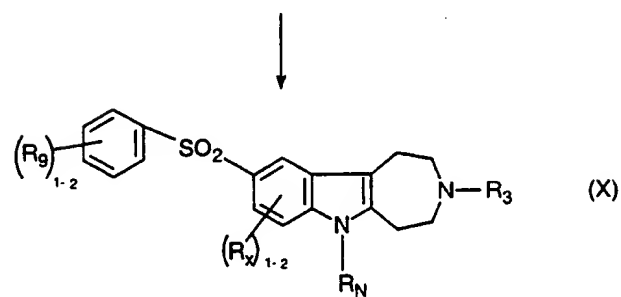
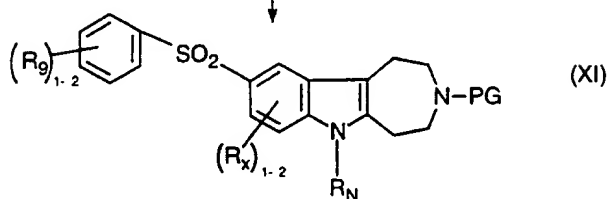
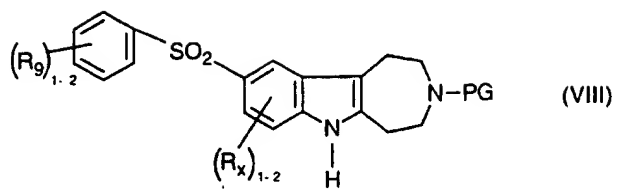


CHART C

5

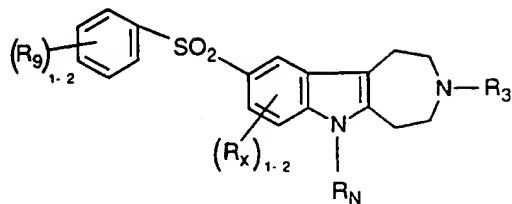


10

15

CLAIMS

1. A 9-arylsulfone of the formula (XII)



5 where  $R_3$  is:

(1) -H,

(2)  $C_1$ - $C_4$  alkyl,

(3)  $C_0$ - $C_4$ - $\phi$  where the  $\phi$  substituent is optionally substituted with 1 or 2

(a) -F, -Cl, -Br, -I,

10 (b) -O- $R_{3-1}$  where  $R_{3-1}$  is:

-H,

$C_1$ - $C_4$  alkyl,

- $\phi$ ,

(c) -CF<sub>3</sub>,

15 (d) -CO-NR<sub>3-2</sub>R<sub>3-3</sub> where  $R_{3-2}$  and  $R_{3-3}$  are -H and  $C_1$ - $C_4$  alkyl, and where  $R_{3-2}$

and  $R_{3-3}$  are taken with the attached nitrogen atom to form a ring selected from the group consisting of 1-pyrrolidinyl, 1-piperazinyl and 1-morpholinyl,

(e) -NH-SO<sub>2</sub>-R<sub>3-4</sub> where  $R_{3-4}$  is -H and  $C_1$ - $C_4$  alkyl,

(f) -NR<sub>3-2</sub>R<sub>3-3</sub> where  $R_{3-2}$  and  $R_{3-3}$  are as defined above,

20 (g) -NR<sub>3-4</sub>-CO-R<sub>3-4</sub> where  $R_{3-4}$  is as defined above,

(h) -SO<sub>2</sub>-NR<sub>3-2</sub>R<sub>3-3</sub> where  $R_{3-2}$  and  $R_{3-3}$  are as defined above,

(i) -C $\equiv$ N,

(j) -NO<sub>2</sub>,

where  $R_N$  is:

25 (1) -H,

(2)  $C_1$ - $C_4$  alkyl,

(3)  $C_0$ - $C_4$ - $\phi$  where the  $\phi$  substituent is optionally substituted with 1 or 2

(a) -F, -Cl, -Br, -I,

(b) -O- $R_{N-1}$  where  $R_{N-1}$  is

30

-H,

C<sub>1</sub>-C<sub>4</sub> alkyl,

-φ,

(c) -CF<sub>3</sub>,

(d) -CO-NR<sub>N-2</sub>R<sub>N-3</sub> where R<sub>N-2</sub> and R<sub>N-3</sub> are -H and C<sub>1</sub>-C<sub>4</sub> alkyl, and where

5 R<sub>3-2</sub> and R<sub>3-3</sub> are taken with the attached nitrogen atom to form a ring selected from the group consisting of 1-pyrrolidinyl, 1-piperazinyl and 1-morpholinyl,

(e) -NH-SO<sub>2</sub>-R<sub>N-4</sub> where R<sub>N-4</sub> is -H and C<sub>1</sub>-C<sub>4</sub> alkyl,

(f) -NR<sub>N-2</sub>R<sub>N-3</sub> where R<sub>N-2</sub> and R<sub>N-3</sub> are as defined above,

(g) -NR<sub>N-4</sub>-CO-R<sub>N-4</sub> where R<sub>N-4</sub> is as defined above,

10 (h) -SO<sub>2</sub>-NR<sub>N-2</sub>R<sub>N-3</sub> where R<sub>N-2</sub> and R<sub>N-3</sub> are as defined above,

(i) -C≡N,

(j) -NO<sub>2</sub>,

where R<sub>X</sub> is:

(1) -H

15 (2) -F, -Cl, -Br, -I,

(3) -O-R<sub>X-1</sub> where R<sub>X-1</sub> is:

-H,

C<sub>1</sub>-C<sub>4</sub> alkyl,

-φ,

20 (4) -CF<sub>3</sub>,

(5) -CO-NR<sub>X-2</sub>R<sub>X-3</sub> where R<sub>X-2</sub> and R<sub>X-3</sub> are as defined above,

(6) -NH-SO<sub>2</sub>-R<sub>X-4</sub> where R<sub>X-4</sub> is as defined above,

(7) -NR<sub>X-2</sub>R<sub>X-3</sub> where R<sub>X-2</sub> and R<sub>X-3</sub> are as defined above,

(8) -NR<sub>X-4</sub>-CO-R<sub>X-4</sub> where R<sub>X-4</sub> is as defined above,

25 (9) -SO<sub>2</sub>-NR<sub>X-2</sub>R<sub>X-3</sub> where R<sub>X-2</sub> and R<sub>X-3</sub> are as defined above,

(10) -C≡N,

(11) -NO<sub>2</sub>;

where R<sub>9</sub> is:

(1) -H,

30 (2) -F, -Cl,

(3) C<sub>1</sub>-C<sub>4</sub> alkyl,

(4) C<sub>1</sub>-C<sub>3</sub> alkoxy,

(5) -CF<sub>3</sub>,

(6) C<sub>0</sub>-C<sub>4</sub>-φ where the -φ substituent is optionally substituted with 1 or 2

(a) -F, -Cl, -Br, -I,

(b) -O-R<sub>9.1</sub> where R<sub>9.1</sub> is:

-H,

C<sub>1</sub>-C<sub>4</sub> alkyl,

-φ,

(c) -CF<sub>3</sub>,

(d) -CO-NR<sub>9.2</sub>R<sub>9.3</sub> where R<sub>9.2</sub> and R<sub>9.3</sub> are -H and C<sub>1</sub>-C<sub>4</sub> alkyl, and where R<sub>9.2</sub> and R<sub>9.3</sub> are taken with the attached nitrogen atom to form a ring selected from the group consisting of 1-pyrrolidinyl, 1-piperazinyl and 1-morpholinyl,

(e) -NH-SO<sub>2</sub>-R<sub>9.4</sub> where R<sub>9.4</sub> is -H and C<sub>1</sub>-C<sub>4</sub> alkyl,

(f) -NR<sub>9.2</sub>R<sub>9.3</sub> where R<sub>9.2</sub> and R<sub>9.3</sub> are as defined above,

(g) -NR<sub>9.4</sub>-CO-R<sub>9.4</sub> where R<sub>9.4</sub> is as defined above,

(h) -SO<sub>2</sub>-NR<sub>9.2</sub>R<sub>9.3</sub> where R<sub>9.2</sub> and R<sub>9.3</sub> are as defined above,

(i) -C≡N,

(j) -NO<sub>2</sub>

(7) -OR<sub>9.1</sub> where R<sub>9.1</sub> is as defined above,

(8) -CO-NR<sub>9.2</sub>R<sub>9.3</sub> where R<sub>9.2</sub> and R<sub>9.3</sub> are as defined above,

(9) -NR<sub>9.2</sub>R<sub>9.3</sub> where R<sub>9.2</sub> and R<sub>9.3</sub> are as defined above,

(10) -NH-SO<sub>2</sub>-R<sub>9.4</sub> where R<sub>9.4</sub> is as defined above,

(11) -NH-CO<sub>2</sub>-R<sub>9.2</sub> where R<sub>9.2</sub> is as defined above and pharmaceutically acceptable salts thereof.

2. A 9-arylsulfone (XII) according to claim 1 where R<sub>3</sub> is selected from the group consisting of -H and C<sub>1</sub>-C<sub>2</sub> alkyl.

3. 9-arylsulfone (XII) according to claim 2 where R<sub>3</sub> is -H.

4. A 9-arylsulfone (XII) according to claim 1 where R<sub>N</sub> is selected from the group consisting of -H and C<sub>1</sub>-C<sub>4</sub> alkyl.

5. A 9-arylsulfone (XII) according to claim 4 where R<sub>N</sub> is -H, C<sub>1</sub> alkyl and C<sub>2</sub> alkyl.

6. A 9-arylsulfone (XII) according to claim 1 where R<sub>x</sub> is selected from the group consisting of -H, -F and -Cl.

7. A 9-arylsulfone (XII) according to claim 6 where  $R_x$  is  $-H$ .
8. A 9-arylsulfone (XII) according to claim 1 where  $R_9$  is selected from the group consisting  
5 of  $-H$ ,  $-F$ ,  $-Cl$ ,  $C_1-C_3$  alkyl,  $C_1-C_3$  alkoxy and  $-CF_3$ .
9. A 9-arylsulfone (XII) according to claim 8 where  $R_9$  is  $-H$ ,  $-F$ ,  $-Cl$ ,  $C_1$  alkyl,  $C_1$  alkoxy, and  $-CF_3$ .
10. A 9-arylsulfone (XII) according to claim 8 where the  $R_9$  substituent is in the 3- or 4-  
10 position.
11. A 9-arylsulfone (XII) according to claim 1 where the pharmaceutically acceptable salt is  
selected from the group consisting of salts of methanesulfonic, hydrochloric, hydrobromic,  
15 sulfuric, phosphoric, nitric, benzoic, citric, tartaric, fumaric, maleic,  $CH_3-(CH_2)_n-COOH$   
where  $n$  is 0 thru 4,  $HOOC-(CH_2)_n-COOH$  where  $n$  is as defined above.
12. A 9-arylsulfone (XII) according to claim 11 where the pharmaceutically acceptable salt  
is selected from the group consisting of salts of hydrochloric, maleate and methanesulfonic  
20 acids.
13. A 9-arylsulfone (XII) according to claim 12 where the pharmaceutically acceptable salt  
is the salt of hydrochloric acid.
14. A 9-arylsulfone (XII) according to claim 1 where the substituted 9-arylsulfone is  
25 selected from the group consisting of:
- 9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,
  - 9-[(4-fluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,
  - 9-[(4-methylphenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,
  - 30 9-[(4-methoxyphenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,
  - 9-[(3-fluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,
  - 9-[(3-methoxyphenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,
  - 9-[(4-trifluoromethylphenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,
  - 6-ethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,



- 6-ethyl-9-[(4-fluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 6-methyl-9-[(4-fluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 6-methyl-9-[(4-trifluoromethylphenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-  
 b]indole,  
 5 6-ethyl-9-[(4-trifluoromethylphenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-  
 b]indole and  
 6-methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole.

15. A 9-arylsulfone (XII) according to claim 14 where the substituted 9-arylsulfone is 6-  
 10 methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole.

16. A 9-arylsulfone (XII) according to claim 1 where the substituted 9-arylsulfone is  
 selected from the group consisting of:

- 9-[(3,4-difluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 15 9-[(3,5-difluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 9-[(3,5-difluorophenyl)sulfonyl]-6-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
 b]indole,  
 9-[(4-(2-hydroxyethoxy)phenyl)sulfonyl]-6-methyl-1,2,3,4,5,6-  
 hexahydroazepino[4,5-b]indole,  
 20 3,6-dimethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 3-methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole and  
 9-[(4-fluorophenyl)sulfonyl]-3-isopropyl-6-methyl-1,2,3,4,5,6-  
 hexahydroazepino[4,5-b]indole.

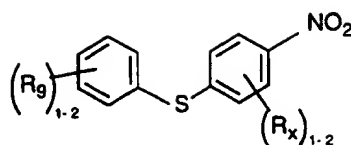
25 17. A 9-arylsulfone (XII) according to claim 1 where the substituted 9-arylsulfone is  
 selected from the group consisting of:

- 1-methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 2-methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 4-methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 30 5-methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 9-[(4-fluorophenyl)sulfonyl]-1-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 9-[(4-fluorophenyl)sulfonyl]-2-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 9-[(4-fluorophenyl)sulfonyl]-4-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 9-[(4-fluorophenyl)sulfonyl]-5-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,

- 1,6-dimethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
2,6-dimethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
4,6-dimethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
5,6-dimethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
5 9-[(4-fluorophenyl)sulfonyl]-1,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole,  
9-[(4-fluorophenyl)sulfonyl]-2,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole,  
9-[(4-fluorophenyl)sulfonyl]-4,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
10 b]indole,  
9-[(4-fluorophenyl)sulfonyl]-5,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole,  
9-[(3,5-difluorophenyl)sulfonyl]-1-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole,  
15 9-[(3,5-difluorophenyl)sulfonyl]-2-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole,  
9-[(3,5-difluorophenyl)sulfonyl]-4-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole,  
9-[(3,5-difluorophenyl)sulfonyl]-5-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
20 b]indole,  
9-[(3,5-difluorophenyl)sulfonyl]-1,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole,  
9-[(3,5-difluorophenyl)sulfonyl]-2,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole,  
25 9-[(3,5-difluorophenyl)sulfonyl]-4,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole,  
9-[(3,5-difluorophenyl)sulfonyl]-5,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole.

30

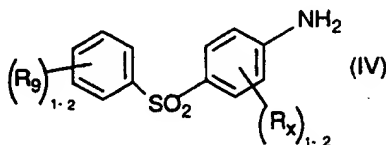
18. A thio ether of formula (III)



where  $R_9$  and  $R_x$  are as defined in claim 1.

19. A thio ether according to claim 18 where  $R_9$  is selected from the group consisting of -H, -F, -Cl,  $C_1$ - $C_3$  alkyl,  $C_1$ - $C_3$  alkoxy and  $-CF_3$  and where  $R_x$  is selected from the group consisting of -H, -F and -Cl.

20. An amine of formula (IV)

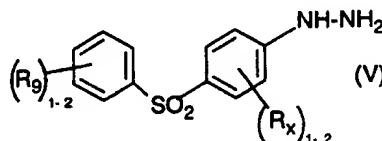


10

where  $R_9$  and  $R_x$  are as defined in claim 1.

21. An amine according to claim 20 where  $R_9$  and  $R_x$  are as defined in claim 19.

22. A hydrazine of formula (V)

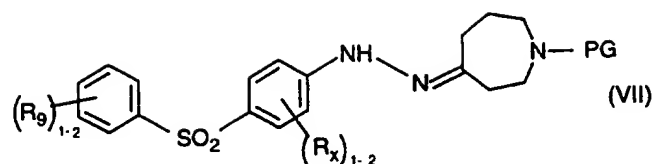


where  $R_9$  and  $R_x$  are as defined in claim 1.

23. A hydrazine according to claim 22 where  $R_9$  and  $R_x$  are as defined in claim 19.

20

24. A compound of formula (VII)

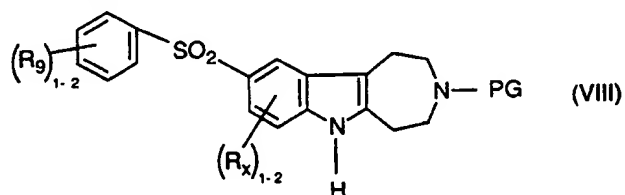


where PG is selected from the group consisting of  $\phi$ -CH<sub>2</sub>-,  $\phi$ -CO-,  $\phi$ -CH<sub>2</sub>-CO<sub>2</sub>- and -CO-O-C(CH<sub>3</sub>)<sub>3</sub> where R<sub>9</sub> and R<sub>x</sub> are as defined in claim 1.

5

25. A compound according to claim 24 where PG is  $\phi$ -CH<sub>2</sub>- or  $\phi$ -CO- and where R<sub>9</sub> and R<sub>x</sub> are as defined in claim 19.

26. A protected 9-arylsulfone of formula (VIII)



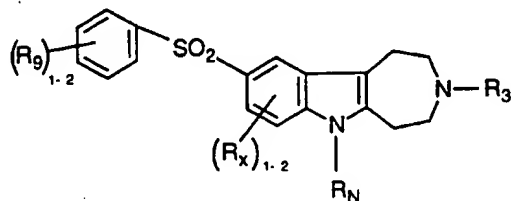
10

where PG is as defined in claim 24 and R<sub>9</sub> and R<sub>x</sub> are as defined in claim 1.

27. A protected 9-arylsulfone according to claim 26 where PG is as defined in claim 25 and where R<sub>9</sub> and R<sub>x</sub> are as defined in claim 19.

15

28. The use of a 9-arylsulfone of the formula (XII)



where R<sub>3</sub> is:

(1) -H,

(2) C<sub>1</sub>-C<sub>4</sub> alkyl,

(3) C<sub>0</sub>-C<sub>4</sub>- $\phi$  where the - $\phi$  substituent is optionally substituted with 1 or 2

(a) -F, -Cl, -Br, -I,

(b) -O-R<sub>3-1</sub> where R<sub>3-1</sub> is:

20

- H,
- C<sub>1</sub>-C<sub>4</sub> alkyl,
- $\phi$ ,
- (c) -CF<sub>3</sub>,
- 5 (d) -CO-NR<sub>3.2</sub>R<sub>3.3</sub> where R<sub>3.2</sub> and R<sub>3.3</sub> are -H and C<sub>1</sub>-C<sub>4</sub> alkyl, and where R<sub>3.2</sub> and R<sub>3.3</sub> are taken with the attached nitrogen atom to form a ring selected from the group consisting of 1-pyrrolidinyl, 1-piperazinyl and 1-morpholinyl,
- (e) -NH-SO<sub>2</sub>-R<sub>3.4</sub> where R<sub>3.4</sub> is -H and C<sub>1</sub>-C<sub>4</sub> alkyl,
- (f) -NR<sub>3.2</sub>R<sub>3.3</sub> where R<sub>3.2</sub> and R<sub>3.3</sub> are as defined above,
- 10 (g) -NR<sub>3.4</sub>-CO-R<sub>3.4</sub> where R<sub>3.4</sub> is as defined above,
- (h) -SO<sub>2</sub>-NR<sub>3.2</sub>R<sub>3.3</sub> where R<sub>3.2</sub> and R<sub>3.3</sub> are as defined above,
- (I) -C $\equiv$ N,
- (j) -NO<sub>2</sub>,

where R<sub>N</sub> is:

- 15 (1) -H,
- (2) C<sub>1</sub>-C<sub>4</sub> alkyl,
- (3) C<sub>0</sub>-C<sub>4</sub>- $\phi$  where the - $\phi$  substituent is optionally substituted with 1 or 2
  - (a) -F, -Cl, -Br, -I,
  - (b) -O-R<sub>N-1</sub> where R<sub>N-1</sub> is
    - 20 -H,
    - C<sub>1</sub>-C<sub>4</sub> alkyl,
    - $\phi$ ,
    - (c) -CF<sub>3</sub>,
    - (d) -CO-NR<sub>N-2</sub>R<sub>N-3</sub> where R<sub>N-2</sub> and R<sub>N-3</sub> are -H and C<sub>1</sub>-C<sub>4</sub> alkyl, and where
      - 25 R<sub>3.2</sub> and R<sub>3.3</sub> are taken with the attached nitrogen atom to form a ring selected from the group consisting of 1-pyrrolidinyl, 1-piperazinyl and 1-morpholinyl,
      - (e) -NH-SO<sub>2</sub>-R<sub>N-4</sub> where R<sub>N-4</sub> is -H and C<sub>1</sub>-C<sub>4</sub> alkyl,
      - (f) -NR<sub>N-2</sub>R<sub>N-3</sub> where R<sub>N-2</sub> and R<sub>N-3</sub> are as defined above,
      - (g) -NR<sub>N-4</sub>-CO-R<sub>N-4</sub> where R<sub>N-4</sub> is as defined above,
      - 30 (h) -SO<sub>2</sub>-NR<sub>N-2</sub>R<sub>N-3</sub> where R<sub>N-2</sub> and R<sub>N-3</sub> are as defined above,
      - (I) -C $\equiv$ N,
      - (j) -NO<sub>2</sub>,

where R<sub>X</sub> is:

(1) -H

(2) -F, -Cl, -Br, -I,

(3) -O-R<sub>X-1</sub> where R<sub>X-1</sub> is:

-H,

5 C<sub>1</sub>-C<sub>4</sub> alkyl,

-φ,

(4) -CF<sub>3</sub>,

(5) -CO-NR<sub>X-2</sub>R<sub>X-3</sub> where R<sub>X-2</sub> and R<sub>X-3</sub> are as defined above,

(6) -NH-SO<sub>2</sub>-R<sub>X-4</sub> where R<sub>X-4</sub> is as defined above,

10 (7) -NR<sub>X-2</sub>R<sub>X-3</sub> where R<sub>X-2</sub> and R<sub>X-3</sub> are as defined above,

(8) -NR<sub>X-4</sub>-CO-R<sub>X-4</sub> where R<sub>X-4</sub> is as defined above,

(9) -SO<sub>2</sub>-NR<sub>X-2</sub>R<sub>X-3</sub> where R<sub>X-2</sub> and R<sub>X-3</sub> are as defined above,

(10) -C≡N,

(11) -NO<sub>2</sub>;

15 where R<sub>9</sub> is:

(1) -H,

(2) -F, -Cl,

(3) C<sub>1</sub>-C<sub>4</sub> alkyl,

(4) C<sub>1</sub>-C<sub>3</sub> alkoxy,

20 (5) -CF<sub>3</sub>,

(6) C<sub>0</sub>-C<sub>4</sub>-φ where the -φ substituent is optionally substituted with 1 or 2

(a) -F, -Cl, -Br, -I,

(b) -O-R<sub>9-1</sub> where R<sub>9-1</sub> is:

-H,

25 C<sub>1</sub>-C<sub>4</sub> alkyl,

-φ,

(c) -CF<sub>3</sub>,

(d) -CO-NR<sub>9-2</sub>R<sub>9-3</sub> where R<sub>9-2</sub> and R<sub>9-3</sub> are -H and C<sub>1</sub>-C<sub>4</sub> alkyl, and where

R<sub>9-2</sub> and R<sub>9-3</sub> are taken with the attached nitrogen atom to form a ring selected from the

30 group consisting of 1-pyrrolidinyl, 1-piperazinyl and 1-morpholinyl,

(e) -NH-SO<sub>2</sub>-R<sub>9-4</sub> where R<sub>9-4</sub> is -H and C<sub>1</sub>-C<sub>4</sub> alkyl,

(f) -NR<sub>9-2</sub>R<sub>9-3</sub> where R<sub>9-2</sub> and R<sub>9-3</sub> are as defined above,

(g) -NR<sub>9-4</sub>-CO-R<sub>9-4</sub> where R<sub>9-4</sub> is as defined above,

(h) -SO<sub>2</sub>-NR<sub>9-2</sub>R<sub>9-3</sub> where R<sub>9-2</sub> and R<sub>9-3</sub> are as defined above,

(l)  $-C\equiv N$ ,

(j)  $-NO_2$

(7)  $-OR_{9.1}$  where  $R_{9.1}$  is as defined above,

(8)  $-CO-NR_{9.2}R_{9.3}$  where  $R_{9.2}$  and  $R_{9.3}$  are as defined above,

5 (9)  $-NR_{9.2}R_{9.3}$  where  $R_{9.2}$  and  $R_{9.3}$  are as defined above,

(10)  $-NH-SO_2-R_{9.4}$  where  $R_{9.4}$  is as defined above,

(11)  $-NH-CO_2-R_{9.2}$  where  $R_{9.2}$  is as defined above,

and pharmaceutically acceptable salts thereof for the manufacture of a medicament for use  
in treating a human who has a condition selected from the group consisting of anxiety,  
10 depression, schizophrenia, stress related disease, panic, a phobia, obsessive compulsive  
disorder, obeisity, post-traumatic stress syndrome and who is in need of such treatment.

29. A medicament according to claim 28 where the condition is anxiety or depression.

15 30. A medicament according to claim 28 where the administered is orally, sublingually,  
transdermally and parenterally.

31. A medicament according to claim 30 where the administration is oral.

20 32. A medicament according to claim 28 where the administration is in divided doses  
either two, three or four times daily.

33. A medicament according to claim 28 where the effective amount is from about 0.1 to  
about 50 mg/kg/day.

25

34. A medicament according to claim 33 where the effective amount is from about 0.1 to  
about 10 mg/kg/day.

30 35. A medicament according to claim 28 where the 9-arylsulfone of the formula (XII) is  
selected from the group consisting of

9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,

9-[(4-fluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,

9-[(4-methylphenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,

9-[(4-methoxyphenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,

- 9-[(3-fluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 9-[(3-methoxyphenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 9-[(4-trifluoromethylphenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 6-ethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 5 6-ethyl-9-[(4-fluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 6-methyl-9-[(4-fluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 6-methyl-9-[(4-trifluoromethylphenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-  
 b]indole,  
 6-ethyl-9-[(4-trifluoromethylphenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-  
 10 b]indole,  
 6-methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 9-[(3,4-difluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 9-[(3,5-difluorophenyl)sulfonyl]-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 9-[(3,5-difluorophenyl)sulfonyl]-6-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
 15 b]indole,  
 9-[(4-(2-hydroxyethoxy)phenyl)sulfonyl]-6-methyl-1,2,3,4,5,6-  
 hexahydroazepino[4,5-b]indole,  
 3,6-dimethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 3-methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole and  
 20 9-[(4-fluorophenyl)sulfonyl]-3-isopropyl-6-methyl-1,2,3,4,5,6-  
 hexahydroazepino[4,5-b]indole.

36. A medicament according to claim 35 where the 9-arylsulfone of the formula (XII) is 6-methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole.

25

37. A medicament according to claim 28 where the 9-arylsulfone of the formula (XII) is selected from the group consisting of

- 1-methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 2-methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 30 4-methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 5-methyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 9-[(4-fluorophenyl)sulfonyl]-1-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 9-[(4-fluorophenyl)sulfonyl]-2-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
 9-[(4-fluorophenyl)sulfonyl]-4-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,



- 9-[(4-fluorophenyl)sulfonyl]-5-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
1,6-dimethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
2,6-dimethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
4,6-dimethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
5 5,6-dimethyl-9-(phenylsulfonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole,  
9-[(4-fluorophenyl)sulfonyl]-1,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole,  
9-[(4-fluorophenyl)sulfonyl]-2,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole,  
10 9-[(4-fluorophenyl)sulfonyl]-4,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole,  
9-[(4-fluorophenyl)sulfonyl]-5,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole,  
9-[(3,5-difluorophenyl)sulfonyl]-1-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
15 b]indole,  
9-[(3,5-difluorophenyl)sulfonyl]-2-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole,  
9-[(3,5-difluorophenyl)sulfonyl]-4-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole,  
20 9-[(3,5-difluorophenyl)sulfonyl]-5-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole,  
9-[(3,5-difluorophenyl)sulfonyl]-1,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole,  
9-[(3,5-difluorophenyl)sulfonyl]-2,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
25 b]indole,  
9-[(3,5-difluorophenyl)sulfonyl]-4,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole,  
9-[(3,5-difluorophenyl)sulfonyl]-5,6-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-  
b]indole.

30

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/16322

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 C07D487/04 A61K31/55 C07C321/30 C07C317/32 C07D223/12  
 //(C07D487/04, 223:00, 209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 028 381 A (SANDOZ AG) 13 May 1981 (1981-05-13) abstract; claims ---	1,28-37
A	US 3 652 588 A (HESTER JACKSON B JR) 28 March 1972 (1972-03-28) cited in the application abstract ---	1,28-37
A	FR 6 699 M (THE UPJOHN COMPANY) 10 February 1969 (1969-02-10) abstract & US 3 839 357 A 1 October 1974 (1974-10-01) cited in the application ---	1,28-37
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

16 October 2000

Date of mailing of the international search report

27/10/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Frelon, D

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 00/16322

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>HESTER J B ET AL: "AZEPINOINDOLES. I. HEXAHYDROAZEPINO4,5-BETAINDOLES" JOURNAL OF MEDICINAL CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 11, no. 1, 1968, pages 101-106, XP000650781 ISSN: 0022-2623 the whole document</p> <p style="text-align: center;">---</p>	1,28-37
A	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ARTEMENKO, G. N. ET AL: "Pharmacological activity spectra of some azepino- and benzoxepinoindole derivatives" retrieved from STN Database accession no. 77:69985 XP002149978 abstract &amp; FARMAKOL. TOKSIKOL. (MOSCOW) (1972), 35(3), 274-80 ,</p> <p style="text-align: center;">---</p>	1,28-37
A	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SHARKOVA, N. M. ET AL: "Indole derivatives. XXIV. Synthesis of some 1,2,3,4,5,6-hexahydroazepino'4,5-b!indoles" retrieved from STN Database accession no. 69:86857 XP002149979 abstract, RNs 19869-47-7;19869-50-2 &amp; KHIM. GETEROTSIKL. SOEDIN. (1968), (1), 131-6 ,</p> <p style="text-align: center;">---</p>	1,28-37
X,P	<p style="text-align: center;">---</p> <p>WO 99 44618 A (BUTLIN ROGER JOHN ;ZENECA LTD (GB)) 10 September 1999 (1999-09-10) methods 15,18</p> <p style="text-align: center;">---</p>	18
X	<p style="text-align: center;">---</p> <p>WO 99 32463 A (BAYER AG) 1 July 1999 (1999-07-01) method A15</p> <p style="text-align: center;">---</p>	18
X	<p style="text-align: center;">---</p> <p>WO 97 13748 A (CHONG KUN DANG CORP ;KIM JUNG WOO (KR); KWON CHUL HOON (US); CHUNG) 17 April 1997 (1997-04-17) example 6</p> <p style="text-align: center;">---</p>	18
X	<p style="text-align: center;">---</p> <p>EP 0 666 253 A (TAISHO PHARMA CO LTD ;MITSUI PETROCHEMICAL IND (JP)) 9 August 1995 (1995-08-09) interm. cmpds page 5; ref. ex. 1</p> <p style="text-align: center;">---</p>	18
	-/--	

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 00/16322

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 354 303 A (AMERICAN CYANAMID CO) 14 February 1990 (1990-02-14) interm. ex. 1,2,6	20
X	interm. ex. 4	18
X	--- EP 0 013 414 A (CELAMERCK GMBH & CO KG) 23 July 1980 (1980-07-23) page 36 -page 37	18
X	--- FR 1 499 717 A (AGRIPAT S.A.) examples 17,21,29	18
X	--- FR 1 489 916 A (FARBENFABRIKEN BAYER AG) 15 November 1967 (1967-11-15) ex. 1, page 5; ex. 2,3,4	18
X	--- CH 619 460 A (CIBA GEIGY AG) 30 September 1980 (1980-09-30) example VI	18
X	--- JP 02 048564 A (SUMITOMO SEIKA CHEM CO LTD) 19 February 1990 (1990-02-19) page 8; examples	18
X	--- GB 1 293 540 A (COALITE AND CHEMICAL PRODUCTS LTD) 18 October 1972 (1972-10-18) examples 7,9	18
X	--- FR 2 230 354 A (BAYER AG) 20 December 1974 (1974-12-20) page 31; example A	20
X	--- FR 2 135 740 A (EXXON RESEARCH ENGINEERING CO) 22 December 1972 (1972-12-22) table I	18
X	table II	20
X	--- FR 2 110 283 A (PFIZER) 2 June 1972 (1972-06-02) cmpds II and table pages 13,15,16	20
X	--- FR 2 053 028 A (MERCK & CO INC) 16 April 1971 (1971-04-16) example 6	18
X,P	--- DE 198 29 357 A (BAYER AG) 5 January 2000 (2000-01-05) examples	18
X	--- DE 38 31 445 A (SEYDEL JOACHIM K PROF DR) 22 March 1990 (1990-03-22) page 3, lines 45,51	20
X	page 4, line 22	18
	---	
	-/--	

# INTERNATIONAL SEARCH REPORT

Internat'l Application No

PCT/US 00/16322

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 30 27 530 A (THOMAE GMBH DR K) 25 February 1982 (1982-02-25) page 33, line 7 and table 1, pages 38,40; ex. 1s, page 56 ---	20
X	DE 27 48 978 A (BASF AG) 3 May 1979 (1979-05-03) cmpds. pages 11,18 ---	18
X	DE 27 07 784 A (SANKIO CHEMICAL CO) 25 August 1977 (1977-08-25) page 46, step (2) ---	18
X	DE 25 09 037 A (BAYER AG) 2 September 1976 (1976-09-02) page 13, lines 12,14-17; pages 63,64 page 16, cmpds (N) ---	20
X	DE 24 38 099 A (BAYER AG) 19 February 1976 (1976-02-19) interm. cmpds (IV) of ex. 1,4 ---	18
X	DE 21 20 708 A (ESSO RESEARCH AND ENGINEERING CO.) 9 November 1972 (1972-11-09) table I table II ---	18
X	US 3 948 987 A (FRIDINGER TOMAS L) 6 April 1976 (1976-04-06) column 2; example 1 ---	20
X	US 3 914 418 A (PATCHETT ARTHUR A ET AL) 21 October 1975 (1975-10-21) col. 8, lines 62 ---	18
X	US 3 576 872 A (SINGHAL GOPAL H) 27 April 1971 (1971-04-27) table I table II ---	20
X	US 4 026 830 A (GILLMAN HYMAN D ET AL) 31 May 1977 (1977-05-31) column 5, line 12 ---	20
X	US 4 239 888 A (MILLER MAX W) 16 December 1980 (1980-12-16) column 12; example 5 ---	18
X	US 4 332 820 A (MARKLEY LOWELL D) 1 June 1982 (1982-06-01) examples 12,20 ---	18
	-/--	

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 00/16322

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 894 358 A (HERCHEN STEPHEN R ET AL) 16 January 1990 (1990-01-16) column 6, line 27 - line 28 ---	18
X	US 5 534 518 A (CHAGUTURU MUNIRATHNAM K ET AL) 9 July 1996 (1996-07-09) interm., col. 10 and ex. 10,82 ---	20
X,P	US 5 952 349 A (GREEN MICHAEL J ET AL) 14 September 1999 (1999-09-14) cmpds IX; ex. 1,3(23) X cmpds X; ex. 2 ---	18
X	WO 94 18980 A (FMC CORP) 1 September 1994 (1994-09-01) interm. compd. No. 82 ---	20
X,P	WO 99 62506 A (BURROWS JEREMY NICHOLAS ;BUTLIN ROGER JOHN (GB); NOWAK THORSTEN (G) 9 December 1999 (1999-12-09) method 27 ---	18
X,P	EP 0 930 302 A (HOFFMANN LA ROCHE) 21 July 1999 (1999-07-21) ex. 61-63 ---	20
X	DE 196 54 445 A (SEYDEL JOACHIM K PROF DR) 2 July 1998 (1998-07-02) page 10 -page 11; table 5 ---	20
X	EP 0 524 781 A (ICI PLC) 27 January 1993 (1993-01-27) ex. 1,2,3a,5,13,14,20,21a,24-32,37a,40a,41,42,44a,45a,49a,52a,58,68 X ex. 3c,4c,40c,44c,49c,52c ---	20
X	JP 60 044557 A (NIPPON KAYAKU KK) 9 March 1985 (1985-03-09) cmpds IV, Nrs. 22-26, page 6 ---	18
X	EP 0 102 476 A (AMERICAN CYANAMID CO) 14 March 1984 (1984-03-14) table I, page 14; ex. 5,12,13,15,16,24,31,35,40,43-47,50 X examples 1-3,18,20,22,37,38,48,49,51,52 ---	20
X	EP 0 035 712 A (BASF AG) 16 September 1981 (1981-09-16) cmpds (II) and ex. Nrs 115,116,119-122 ---	20
X	EP 0 017 883 A (BAYER AG) 29 October 1980 (1980-10-29) examples 7A,10A ---	20
	--- -/--	

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/16322

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 25 48 910 A (BAYER AG) 12 May 1977 (1977-05-12) page 5 ---	18
X	DE 24 38 120 A (BAYER AG) 19 February 1976 (1976-02-19) cmpds (II), table pages 27-31 page 6 ---	20
X	FR 2 154 568 A (BAYER AG) 11 May 1973 (1973-05-11) cmpds (XIII), page 62 ---	18
X	cmpds (XIX), ex, pages 43,48,53,67 ---	20
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HORYNA, JAROSLAV: "Partial reduction of dinitrodiphenyl sulfides, sulfoxides and sulfones" retrieved from STN Database accession no. 105:133513 XP002149980 RN 101-59-7 & CS 229 033 B (CZECH.) 14 May 1984 (1984-05-14) ---	18
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KATIIYAR, MEERA ET AL: "Synthesis and fungitoxicity of some substituted aryl polynitrophenyl sulfides and sulfones" retrieved from STN Database accession no. 97:5890 XP002149981 RN 33668-00-7 & CHIM. ACTA TURC. (1981), 9(2), 395-9 , ---	18
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BEARD, COLIN C. ET AL: "7(8)-Substituted triazinobenzimidazoles having antifungal and anthelmintic activity" retrieved from STN Database accession no. 89:43516 XP002149982 RN 43156-47-4 & ZA 7 603 751 A (SYNTEX , INC., USA) 22 February 1978 (1978-02-22) --- -/--	18

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/16322

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            BARTOLI, G. ET AL: "Electronic and steric            effects in nucleophilic aromatic            substitution. Kinetic studies on the            reactions between ethers and thioethers of            2,4-dinitrophenol and nucleophiles"            retrieved from STN            Database accession no. 84:4033            XP002149983            RNs 2486-09-1;42178-88-1            &amp; J. ORG. CHEM. (1975), 40(25), 3777-8 ,</p>	18
X	<p>---            DATABASE CHEMABS 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            LAKOMOVA, N. A. ET AL:            "2,4-Dinitro-5-amino-1-substituted            benzene"            retrieved from STN            Database accession no. 81:135695            XP002149984            RNs 2486-09-1;53488-26-9            &amp; SU 436 817 T (ALL-UNION            SCIENTIFIC-RESEARCH AND DESIGN INSTITUTE            OF MONOMERS) 25 July 1974 (1974-07-25)</p>	18
X	<p>---            DATABASE CHEMABS 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            SINDELAR, KAREL ET AL: "Substituted benzyl            alcohols"            retrieved from STN            Database accession no. 80:47619            XP002149985            RN 16174-93-9            &amp; CS 149 525 B (SINDELAR, KAREL;PROTIVA,            MIROSLAV) 25 July 1973 (1973-07-25)</p>	18
X	<p>---            DATABASE CHEMABS 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            BIGGI, GINO ET AL: ".sigma.-Complex            formation and aromatic substitution with            thiolates and nitroaryl thio ethers"            retrieved from STN            Database accession no. 80:26525            XP002149986            RN 51030-13-8            &amp; J. CHEM. SOC., PERKIN TRANS. 1 (1973),            (18), 1980-3 ,</p>	18
	<p>---            -/--</p>	



# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 00/16322

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MITAL, R. L. ET AL: "New phenothiazines by Smiles rearrangement" retrieved from STN Database accession no. 71:49874 XP002149987 RN 23416-52-6 &amp; ANN. SOC. SCI. BRUXELLES, SER. 1 (1969), 83(1), 182-96 ,</p>	18
X	<p>--- DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ROHR, OTTO ET AL: "Diphenyl thioether pesticides" retrieved from STN Database accession no. 70:77581 XP002149988 RN 21726-41-0 &amp; ZA 6 801 404 1 (CIBA LTD.) 1 August 1968 (1968-08-01)</p>	18
X	<p>--- DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; LUTSKII, A. E. ET AL: "Interaction of functional groups through pi.-electron systems. V. Interaction through aromatic rings connected by a monofunctional bridging group" retrieved from STN Database accession no. 70:3132 XP002149989 RNs 101-59-7;21969-11-9 &amp; ZH. FIZ. KHIM. (1968), 42(8), 1861-4 ,</p>	18
X	<p>--- DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BARTON, DEREK H. R. ET AL: "Photochemical transformations. XXII. Reactions of 2,4-dinitrobenzenesulfonyl derivatives" retrieved from STN Database accession no. 68:58880 XP002149990 RN 18998-35-1 &amp; J. CHEM. SOC. C (1968), (3), 322-7 ,</p> <p>--- -/--</p>	18

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 00/16322

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; GUPTA, SATYA PRAKASH ET AL: "Potential fungicidal compounds. IV. Some aryl polynitrophenyl sulfones" retrieved from STN Database accession no. 67:32406 XP002149991 RN 14723-62-7 &amp; INDIAN J. APPL. CHEM. (1966), 29(2-3), 51-3 ,</p>	18
X,P	<p>--- DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; DIAZ, FERNANDO R. ET AL: "Synthesis, characterization and electrical properties of poly(p-phenylsulfonyl aniline)" retrieved from STN Database accession no. 133:208265 XP002149992 RN 290341-70-7 &amp; BOL. SOC. CHIL. QUIM. (2000), 45(2), 181-189 ,</p>	20
X	<p>--- DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TINGLE, M. D. ET AL: "The effect of 2,2'-substitution on the metabolism and toxicity of dapsone in vitro and in vivo" retrieved from STN Database accession no. 129:49195 XP002149993 RN 208645-29-8 &amp; ENVIRON. TOXICOL. PHARMACOL. (1998), 5(2), 145-153 ,</p>	20
X	<p>--- DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; DE LA CRUZ, A. ET AL: "Synthesis and antimicrobial evaluation of new derivatives of diphenylsulfone" retrieved from STN Database accession no. 121:200742 XP002149994 RN 158143-82-9 &amp; BOLL. CHIM. FARM. (1994), 133(2), 72-5 ,</p> <p>--- -/--</p>	20

# INTERNATIONAL SEARCH REPORT

Intern: al Application No  
PCT/US 00/16322

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; IDDON, BRIAN ET AL: "2H-Benzimidazoles (isobenzimidazoles). Part 7. A new route to triclabendazole '5-chloro-6-(2,3-dichlorophenoxy)-2-methyl thio-1H- benzimidazole! and congeneric benzimidazoles" retrieved from STN Database accession no. 118:101877 XP002149995 RN 145770-98-5 &amp; J. CHEM. SOC., PERKIN TRANS. 1 (1992), (22), 3129-34 ,</p>	20
X	<p>--- DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; DE BENEDETTI, P. G.: "Electrostatics in quantitative structure-activity relationship analysis" retrieved from STN Database accession no. 117:127091 XP002149996 RN 143352-92-5 &amp; THEOCHEM (1992), 88, 231-48 ,</p>	20
X	<p>--- DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ALLEGRA, CARMEN J. ET AL: "Interaction of sulfonamide and sulfone compounds with Toxoplasma gondii dihydropteroate synthase" retrieved from STN Database accession no. 112:171745 XP002149997 RN 19878-60-5,126348-49-0 &amp; J. CLIN. INVEST. (1990), 85(2), 371-9 ,</p> <p>--- -/--</p>	20

# INTERNATIONAL SEARCH REPORT

Intern: al Application No

PCT/US 00/16322

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            SAXENA, M. ET AL: "Studies on            2,3,N,N'-substituted            4,4'-diaminodiphenylsulfones as potential            antimalarial agents"            retrieved from STN            Database accession no. 111:224808            XP002149998            RNs            6052-22-8;100795_87-7;101586_93-0;101586_9            5-2;101603_02-5;101738-08-3;106882-78-4;10            9090-95-1;109688-83-7;109690-53-1;111294-5            6-5;123862-14-6;123862-36-2;123862-37-3;12            3862-38-4; etc.            &amp; ARZNEIM.-FORSCH. (1989), 39(9), 1081-4 ,</p>	20
X	<p>---            DATABASE CHEMABS 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            DE BENEDETTI, PIER G. ET AL: "Quantitative            structure-activity relationships in            dihydropteroate synthase inhibition by            multisubstituted sulfones. Design and            synthesis of some new derivatives with            improved potency"            retrieved from STN            Database accession no. 111:129562            XP002149999            RN 122443-46-3            &amp; J. MED. CHEM. (1989), 32(10), 2396-9 ,</p>	20
X	<p>---            DATABASE CHEMABS 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            WIESE, M. ET AL: "Multiple regression            analysis of antimalarial activities of            sulfones and sulfonamides in cell-free            systems and principal component analysis            to compare with antibacterial activities"            retrieved from STN            Database accession no. 109:35164            XP002150000            RN 113597-75-4            &amp; QUANT. STRUCT.-ACT. RELAT. (1987), 6(4),            164-72 ,</p> <p>---            -/--</p>	20

# INTERNATIONAL SEARCH REPORT

Intern: al Application No  
PCT/US 00/16322

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KLEIN, A. G. ET AL: "Sulfarylation of ethylbenzene and anisole with p-substituted benzenesulfonic acid salts in phosphoric acid" retrieved from STN Database accession no. 92:110616 XP002150001 RN 73015-23-3;73015-32-4;73015-38-0 &amp; KATALITICH. PREVRASHCHENIYA ORGAN. SOEDIN., PERM (1978) 20-5 FROM: REF. ZH., KHIM. 1979, ABSTR. NO. 23ZH155,</p>	20
X	<p>--- DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; RUSANOV, A. L. ET AL: "Synthesis and study of some bis(1',8'-naphthoylene-1,2- benzimidazoles)" retrieved from STN Database accession no. 92:6465 XP002150002 RN 71625-25-7 &amp; KHIM. GETEROTSIKL. SOEDIN. (1979), (7), 968-71 ,</p>	20
X	<p>--- DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SRINIVASAN, C.: "Fries rearrangement of N-benzenesulfonylaniline" retrieved from STN Database accession no. 88:169736 XP002150003 RN 64896-96-4 &amp; ACTA CIENC. INDICA (1977), 3(1), 18-19 ,</p>	20
X	<p>--- DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; LAPITSKII, V. A. ET AL: "Fireproof polymeric composition" retrieved from STN Database accession no. 84:5940 XP002150004 RN 57171-55-8 &amp; SU 475 382 T (USSR) 30 June 1975 (1975-06-30) --- -/--</p>	20

# INTERNATIONAL SEARCH REPORT

Intern: 91 Application No  
PCT/US 00/16322

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; IVANOV, A. V. ET AL: "Synthesis of 3,4,4'-triaminodiphenyl sulfones and their use in modifying heat-stable fibers" retrieved from STN Database accession no. 80:14687 XP002150005 RN 51224-84-1 &amp; TR. VSES. NAUCH-ISSLED. PROEKT. INST. MONOMEROV (1972), 3(3), 75-80 FROM: REF. ZH., KHIM. 1973, ABSTR. NO. 6N208,</p>	20
X	<p>----- DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KORSHAK, V. V. ET AL: "3,4,4'-Triaminodiphenylsulfone" retrieved from STN Database accession no. 79:66011 XP002150006 RN 41890-39-5 &amp; SU 380 644 T (BURYAT INSTITUTE OF NATURAL SCIENCES) 15 May 1973 (1973-05-15)</p>	20
X	<p>----- DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MONTAUDO, G. ET AL: "NMR data and conformational preference of o-substituted diphenyl sulfones" retrieved from STN Database accession no. 79:4508 XP002150007 RN 42086-00-0 &amp; J. MOL. STRUCT. (1973), 16(2), 299-306 ,</p>	20
X	<p>----- DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BUDNII, I. V. ET AL: "Synthesis of some substituted diphenyl sulfones" retrieved from STN Database accession no. 78:83962 XP002150008 RN 40179-03-1 &amp; ZH. PRIKL. KHIM. (LENINGRAD) (1972), 45(12), 2704-10 ,</p> <p>----- -/--</p>	20

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/16322

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            POPOFF, IVAN C. ET AL: "Antimalarial            agents. 8. Ring-substituted            bis(4-aminophenyl) sulfones and their            precursors"            retrieved from STN            Database accession no. 76:94447            XP002150009            RNs 5914-09-0;20643-77-0            &amp; J. MED. CHEM. (1971), 14(12), 1166-9 ,</p>	20
X	<p>---            DATABASE CHEMABS 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            GILBERT, EVERETT E.: "Aminoaryl sulfones.            New preparative procedure"            retrieved from STN            Database accession no. 75:109988            XP002150010            RN 33597-76-1            &amp; SYNTHESIS (1971), (7), 372-4 ,</p>	20
X	<p>---            DATABASE CHEMABS 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            SHARGHI, N. ET AL:            "o-Trifluoromethylthiophenol and its            derivatives"            retrieved from STN            Database accession no. 66:10690            XP002150011            RN 13334-15-1            &amp; J. CHEM. ENG. DATA (1966), 11(4), 612-14            ,</p>	20
X	<p>---            DATABASE CHEMABS 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            FUJISAWA PHARMACEUTICAL CO., LTD., JAPAN:            "Preparation of biphenyl compounds as            drugs"            retrieved from STN            Database accession no. 115:114130            XP002150012            RN 135209-32-4            &amp; JP 03 056431 A (FUJISAWA PHARMACEUTICAL            CO., LTD., JAPAN)            12 March 1991 (1991-03-12)            ---            -/--</p>	20

# INTERNATIONAL SEARCH REPORT

Intern: al Application No

PCT/US 00/16322

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 282 448 A (CIBA GEIGY AG) 14 September 1988 (1988-09-14) example 209	20
X	example 201	22
X	US 4 298 676 A (BARTON DEREK H R ET AL) 3 November 1981 (1981-11-03) column 10	22
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MIRZIASHVILI, N. T. ET AL: "Synthesis of 5-(p-chlorophenyl)sulfonylindoles" retrieved from STN Database accession no. 115:71307 XP002150013 RN 100062-12-2 & KHIM. GETEROTSIKL. SOEDIN. (1991), (1), 54-6 ,	22
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MOORE, JAMES A. ET AL: "A novel route to polypyrazoles" retrieved from STN Database accession no. 109:74034 XP002150014 RN 70714-83-9 & MACROMOLECULES (1988), 21(8), 2644-7 ,	22
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BADER, HENRY ET AL: "Antimalarial compounds related to diaminodiphenyl sulfone" retrieved from STN Database accession no. 71:49448 XP002150015 RN 17929-52-1 & J. MED. CHEM. (1969), 12, 709-11 ,	22



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/16322

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0028381	A	13-05-1981	AT 12641 T	15-04-1985
			AU 6401480 A	07-05-1981
			DE 3070467 D	15-05-1985
			DK 465380 A	03-05-1981
			ES 496451 D	16-06-1982
			ES 8205800 A	01-11-1982
			FI 803356 A	03-05-1981
			IL 61382 A	29-02-1984
			JP 56075493 A	22-06-1981
			NZ 195423 A	06-07-1984
			PT 72002 A, B	01-11-1980
			US 4478750 A	23-10-1984
			ZA 8006741 A	26-05-1982
US 3652588	A	28-03-1972	NONE	
FR 6699	M	10-02-1969	BE 698268 A	10-11-1967
			CH 506543 A	30-04-1971
			DE 1695943 A	13-05-1971
			ES 340258 A	01-06-1968
			FR 1524495 A	02-09-1968
			GB 1180615 A	04-02-1970
			GB 1180616 A	04-02-1970
			IL 27776 A	29-11-1971
			IL 36801 A	29-11-1971
			NL 6706513 A	13-11-1967
			US 3839357 A	01-10-1974
WO 9944618	A	10-09-1999	AU 3262599 A	20-09-1999
WO 9932463	A	01-07-1999	AU 1939999 A	12-07-1999
			EP 1042305 A	11-10-2000
WO 9713748	A	17-04-1997	AU 7340696 A	30-04-1997
EP 0666253	A	09-08-1995	AU 5285993 A	09-05-1994
			CA 2147495 A	28-04-1994
			WO 9408956 A	28-04-1994
EP 0354303	A	14-02-1990	AU 604607 B	20-12-1990
			AU 3490589 A	23-11-1989
			DD 289521 A	02-05-1991
			DK 242289 A	20-11-1989
			FI 892397 A	20-11-1989
			HU 53355 A, B	28-10-1990
			JP 2022261 A	25-01-1990
			NO 891986 A	20-11-1989
			PL 279554 A	08-01-1990
			PT 90587 A	30-11-1989
			ZA 8903737 A	31-01-1990
EP 0013414	A	23-07-1980	DE 2901334 A	31-07-1980
			DE 2927123 A	08-01-1981
			AR 223695 A	15-09-1981
			AT 1236 T	15-07-1982
			AU 526976 B	10-02-1983
			AU 5463480 A	24-07-1980
			BR 8000223 A	21-10-1980

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/16322

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0013414 A		CA 1126293 A	22-06-1982
		CS 212335 B	26-03-1982
		DD 150459 A	02-09-1981
		DE 2963203 D	12-08-1982
		DK 15080 A	16-07-1980
		ES 487668 D	16-12-1980
		ES 8107174 A	16-12-1981
		ES 493984 D	01-08-1981
		ES 8106700 A	16-11-1981
		ES 493985 D	01-11-1981
		ES 8200651 A	01-02-1982
		GR 73690 A	02-04-1984
		HU 182085 B	28-12-1983
		JP 55098153 A	25-07-1980
		NZ 192596 A	07-09-1982
		PL 221363 A	15-12-1980
		TR 20799 A	17-08-1982
		US 4275077 A	23-06-1981
		YU 6780 A	30-09-1983
		ZA 8000223 A	30-09-1981
FR 1499717 A		CH 462847 A	
		DE 1543326 A	25-09-1969
		GB 1170098 A	12-11-1969
		IL 26841 A	17-09-1970
		MY 22773 A	31-12-1973
		US 3506767 A	14-04-1970
FR 1489916 A	15-11-1967	BE 684391 A	20-01-1967
		DE 1493728 A	28-08-1969
		GB 1156005 A	25-06-1969
CH 619460 A	30-09-1980	NONE	
JP 02048564 A	19-02-1990	NONE	
GB 1293540 A	18-10-1972	CH 523858 A	15-06-1972
FR 2230354 A	20-12-1974	DE 2313721 A	03-10-1974
		AU 475802 B	02-09-1976
		AU 6681174 A	25-09-1975
		BE 812549 A	20-09-1974
		CA 1008860 A	19-04-1977
		CH 605848 A	13-10-1978
		GB 1425789 A	18-02-1976
		HU 168729 B	28-07-1976
		IE 39078 B	02-08-1978
		JP 49125382 A	30-11-1974
		JP 49125511 A	02-12-1974
		LU 69647 A	17-10-1974
		NL 7403613 A	24-09-1974
		SU 531487 A	05-10-1976
		US 3948893 A	06-04-1976
		US 3970752 A	20-07-1976
		ZA 7401772 A	29-01-1975
FR 2135740 A	22-12-1972	NONE	

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/16322

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2110283 A	02-06-1972	AR 195271 A	28-09-1973
		AR 196001 A	23-11-1973
		AT 325629 B	27-10-1975
		AT 866971 A	15-01-1975
		AU 3434771 A	12-04-1973
		BE 773583 A	07-04-1972
		CA 992538 A	06-07-1976
		CH 566328 A	15-09-1975
		CH 563375 A	30-06-1975
		DE 2149645 A	14-09-1972
		ES 395778 A	01-10-1974
		HU 166467 B	28-03-1975
		IT 1050658 B	20-03-1981
		NL 7113797 A	11-04-1972
		ZA 7106613 A	28-06-1972
		GB 1371907 A	30-10-1974
		US 3905971 A	16-09-1975
		US 3912723 A	14-10-1975
FR 2053028 A	16-04-1971	CA 952913 A	13-08-1974
		CH 549008 A	15-05-1974
		GB 1285398 A	16-08-1972
		NL 7008628 A	29-12-1970
		US 3674875 A	04-07-1972
		US 3655697 A	11-04-1972
		US 3759948 A	18-09-1973
DE 19829357 A	05-01-2000	AU 4614399 A	24-01-2000
		WO 0001669 A	13-01-2000
DE 3831445 A	22-03-1990	NONE	
DE 3027530 A	25-02-1982	NONE	
DE 2748978 A	03-05-1979	NONE	
DE 2707784 A	25-08-1977	JP 1172027 C	17-10-1983
		JP 52106871 A	07-09-1977
		JP 57057064 B	02-12-1982
		JP 1218900 C	26-07-1984
		JP 52106872 A	07-09-1977
		JP 58051967 B	19-11-1983
		JP 1098209 C	27-05-1982
		JP 52106873 A	07-09-1977
		JP 56040176 B	18-09-1981
		JP 1016988 C	28-10-1980
		JP 53079869 A	14-07-1978
		JP 55007473 B	26-02-1980
		GB 1561230 A	13-02-1980
		US 4122089 A	24-10-1978
DE 2509037 A	02-09-1976	NONE	
DE 2438099 A	19-02-1976	NONE	
DE 2120708 A	09-11-1972	NONE	
US 3948987 A	06-04-1976	NONE	

# INTERNATIONAL SEARCH REPORT

information on patent family members

Intern. Appl. Application No

PCT/US 00/16322

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3914418 A	21-10-1975	NONE	
US 3576872 A	27-04-1971	GB 1344735 A US 3753679 A	23-01-1974 21-08-1973
US 4026830 A	31-05-1977	NONE	
US 4239888 A	16-12-1980	NONE	
US 4332820 A	01-06-1982	US 4254144 A AR 227410 A AT 9579 T AU 539619 B AU 6660081 A BR 8100427 A CA 1159470 A CS 219350 B DE 3166225 D DK 31481 A,B, EP 0034263 A ES 498762 D ES 8201123 A FI 810201 A GB 2067998 A,B GR 73660 A IE 50836 B IL 61937 A JP 1011015 B JP 1530906 C JP 56110658 A NO 810245 A,B, NZ 196066 A PH 16434 A PL 229385 A PT 72378 A,B ZA 8100447 A	03-03-1981 29-10-1982 15-10-1984 11-10-1984 30-07-1981 11-08-1981 27-12-1983 25-03-1983 31-10-1984 26-07-1981 26-08-1981 01-12-1981 01-03-1982 26-07-1981 05-08-1981 28-03-1984 23-07-1986 30-12-1983 23-02-1989 15-11-1989 01-09-1981 27-07-1981 31-05-1984 07-10-1983 13-04-1982 01-02-1981 25-08-1982
US 4894358 A	16-01-1990	NONE	
US 5534518 A	09-07-1996	US 5616718 A US 5874579 A AP 506 A AP 507 A AU 6298694 A EP 0684824 A MX 9401249 A WO 9418980 A ZA 9401038 A	01-04-1997 23-02-1999 18-07-1996 18-07-1996 14-09-1994 06-12-1995 31-08-1994 01-09-1994 25-08-1994
US 5952349 A	14-09-1999	NONE	
WO 9418980 A	01-09-1994	AP 506 A AP 507 A AU 6298694 A EP 0684824 A MX 9401249 A US 5534518 A US 5616718 A	18-07-1996 18-07-1996 14-09-1994 06-12-1995 31-08-1994 09-07-1996 01-04-1997

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/16322

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9418980 A		US 5874579 A ZA 9401038 A	23-02-1999 25-08-1994
WO 9962506 A	09-12-1999	AU 4052499 A	20-12-1999
EP 0930302 A	21-07-1999	AU 1211099 A BR 9900065 A CN 1231287 A CZ 9900120 A HR 990011 A HU 9900120 A JP 2000053635 A NO 990187 A PL 330841 A US 5990105 A	05-08-1999 09-05-2000 13-10-1999 11-08-1999 31-10-1999 29-11-1999 22-02-2000 19-07-1999 19-07-1999 23-11-1999
DE 19654445 A	02-07-1998	NONE	
EP 0524781 A	27-01-1993	AT 136027 T AU 648423 B AU 2047692 A CA 2074605 A CN 1069727 A, B CZ 282503 B DE 69209395 D DE 69209395 T DK 524781 T ES 2084944 T FI 923379 A GR 3019446 T HK 1003570 A HU 213605 B HU 9500228 A IE 72507 B IL 102626 A JP 5286915 A KR 239077 B MX 9204355 A NO 178300 B NZ 243686 A PL 171933 B PL 171991 B SG 48002 A SK 234292 A RU 2074173 C US 5382598 A US 5474999 A US 5565477 A US 5567735 A US 5565465 A US 5684198 A US 5272163 A ZA 9205559 A	15-04-1996 21-04-1994 28-01-1993 26-01-1993 10-03-1993 16-07-1997 02-05-1996 17-10-1996 12-08-1996 16-05-1996 26-01-1993 30-06-1996 30-10-1998 28-08-1997 28-08-1995 23-04-1997 05-12-1996 02-11-1993 15-01-2000 01-04-1993 20-11-1995 27-04-1995 31-07-1997 31-07-1997 17-04-1998 08-03-1995 27-02-1997 17-01-1995 12-12-1995 15-10-1996 22-10-1996 15-10-1996 04-11-1997 21-12-1993 31-03-1993
JP 60044557 A	09-03-1985	NONE	
EP 0102476 A	14-03-1984	AT 23268 T CA 1215990 A	15-11-1986 30-12-1986

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/16322

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0102476 A		CA 1230057 C	08-12-1987
		DE 3367327 D	11-12-1986
		ES 524772 D	01-06-1985
		ES 8505642 A	01-10-1985
		HK 38190 A	25-05-1990
		JP 59046261 A	15-03-1984
		KR 9008116 B	31-10-1990
		ZA 8305783 A	25-04-1984
		PH 18919 A	08-11-1985
		US 4532349 A	30-07-1985
EP 0035712 A	16-09-1981	DE 3008985 A	01-10-1981
		AR 231436 A	30-11-1984
		AT 2518 T	15-03-1983
		AU 6814081 A	17-09-1981
		BR 8101208 A	08-09-1981
		CA 1172260 A	07-08-1984
		CS 226423 B	19-03-1984
		DD 156665 A	15-09-1982
		DE 3160069 D	24-03-1983
		DK 101681 A	09-09-1981
		HU 185861 B	28-04-1985
		IL 62094 A	31-12-1984
		JP 56139449 A	30-10-1981
		PL 230021 A	23-12-1981
		SU 978713 A	30-11-1982
		US 4396418 A	02-08-1983
		ZA 8101502 A	28-04-1982
EP 0017883 A	29-10-1980	DE 2916135 A	30-10-1980
		AT 322 T	15-11-1981
		AU 532064 B	15-09-1983
		AU 5760480 A	23-10-1980
		CA 1130304 A	24-08-1982
		DE 3060042 D	24-12-1981
		ES 490705 D	16-04-1981
		ES 8104207 A	01-07-1981
		JP 56043259 A	21-04-1981
		US 4387057 A	07-06-1983
		ZA 8002321 A	30-09-1981
DE 2548910 A	12-05-1977	NONE	
DE 2438120 A	19-02-1976	ES 544777 D	01-02-1986
FR 2154568 A	11-05-1973	DE 2147781 A	29-03-1973
		AT 317177 B	12-08-1974
		AU 456553 B	02-12-1974
		AU 4695772 A	28-03-1974
		BE 789138 A	22-03-1973
		DD 103891 A	12-02-1974
		GB 1371969 A	30-10-1974
		HU 165298 B	28-08-1974
		JP 48039614 A	11-06-1973
		JP 48039453 A	09-06-1973
		NL 7212793 A	27-03-1973
		ZA 7206484 A	27-06-1973

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/us 00/16322

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
CS 229033	B	14-05-1984	NONE	
ZA 7603751	A	22-02-1978	AU 1512776 A GB 1522076 A NZ 181231 A US 4011320 A	05-01-1978 23-08-1978 02-06-1978 08-03-1977
SU 436817	T		NONE	
CS 149525	B	25-07-1973	NONE	
ZA 6801404	1		NONE	
SU 475382	T		NONE	
SU 380644	T		NONE	
JP 3056431	A	12-03-1991	NONE	
EP 0282448	A	14-09-1988	JP 63227571 A US 4904794 A	21-09-1988 27-02-1990
US 4298676	A	03-11-1981	US 4621156 A	04-11-1986